EVIDENCE EVALUATIONS FOR AUSTRALIAN DRINKING WATER GUIDELINES CHEMICAL FACT SHEETS - LEAD REPLACEMENTS IN PLUMBING

Silicon Technical Report

Prepared for:

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BASIS OF REPORT

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DOCUMENT CONTROL

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Abbreviations/Definitions

Acronym	Definition
AAS	Atomic Absorption Spectrophotometry
ANOVA	Analysis of Variance
APVMA	Australian Pesticides and Veterinary Medicines Authority
ATSDR	US Agency for Toxic Substances and Disease Registry
$BMDL_{10}$	Benchmark Dose Limit at 10% for 10% extra risk
CaS	Case Study
Co	Cohort
CrSe	Cross-sectional Study
DWG	Drinking Water Guideline
EA	Experimental Animal (Study)
EFSA	European Food Safety Authority
FSANZ	Food Standards Australia New Zealand
HCT	Human Controlled Trial
ICP-MS(AES)	Inductively Coupled Plasma Mass Spectrometry (Atomic Emission Spectroscopy)
IPCS	International Programme on Chemical Safety
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kg bw	Kilogram of Body Weight
LD_{50}	Median Lethal Dose
LOAEL	Lowest Observed Adverse Effect Level
LOR	Limit of Reporting
mL	Millilitre
NHMRC	National Health and Medical Research Council
NOAEL	No Observed Adverse Effect Level
OEHHA	Californian Office of Environmental Health and Hazard Assessment
OHAT	United States Office of Health Assessment and Translation
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RO	Reverse Osmosis
RoB	Risk of Bias
RR	Relative Risk
SAS	Synthetic Amorphous Silica
Si	Silicon
SiO_2	Silicon Dioxide

Acronym	Definition
The Committee	NHMRC Water Quality Advisory Committee
The Guidelines	NHMRC and NRMMC (2011). Australian Drinking Water Guidelines 6 2011; Version 3.8 updated September 2022, National Health and Medical Research Council and Natural Resource Management Ministerial Council, Commonwealth of Australia, Canberra.
TRV	Toxicity Reference Value
US EPA	United States Environmental Protection Agency
WHO	World Health Organization

1 Introduction and Background

The National Health and Medical Research Council (NHMRC) has contracted SLR Consulting Australia Pty Ltd (SLR) to evaluate the existing guidance and evidence for several substances that have been flagged as potential lead replacement alloys in plumbing products in Australia, specifically bismuth, silicon, and selenium; lead is also included as an additional substance for review. The findings of these reviews are intended to be used by NHMRC to develop public health advice and/or health-based guideline values (if required) for inclusion in the *Australian Drinking Water Guidelines* (2011) (the Guidelines). The evidence reviews undertaken by SLR were governed by a newly designed methodological framework intended to implement best practice methods for evidence evaluations as per the 2016 *NHMRC Standards for Guidelines*. For each of the four substances, SLR was asked to:

- Customise and apply the 'Research Protocol' template provided by NHMRC to answer research questions. The research questions and specific requirements for the review varied slightly according to the substance being evaluated.
- Produce a Technical Report and an Evaluation Report for each substance.
  - The Technical Report is to capture the details and methods used to undertake each review.
  - The Evaluation Report is to interpret, synthesise and summarise the existing guidance and evidence pertaining to the research questions.

These tasks were performed in consultation with the NHMRC Water Quality Advisory Committee (the Committee) and NHMRC.

For bismuth and silicon (which currently do not have existing chemical factsheets in the Guidelines), the requirements of the evaluation were as follows:

1. Screen any existing guidance/guidelines on bismuth / bismuth brasses and silicon / silicon brasses (if available).
2. Review all primary studies and other relevant data.
3. Collate and review any useful supporting information for a potential chemical factsheet.

For the other two substances (lead and selenium), requirements 1 and 3 were completed in July 2022.

The report herein is the Technical Report for silicon.

2 Research Questions

Research questions for this review were drafted by SLR and peer reviewed and agreed upon by the Committee and NHMRC prior to conducting the search. They are provided in **Table 1**.

Table 1 Research Questions for Evidence Evaluation of Silicon

#	Research Questions
Health-based	
1	What level of silicon in drinking water causes adverse health effects?
2	What is the endpoint that determines this value?

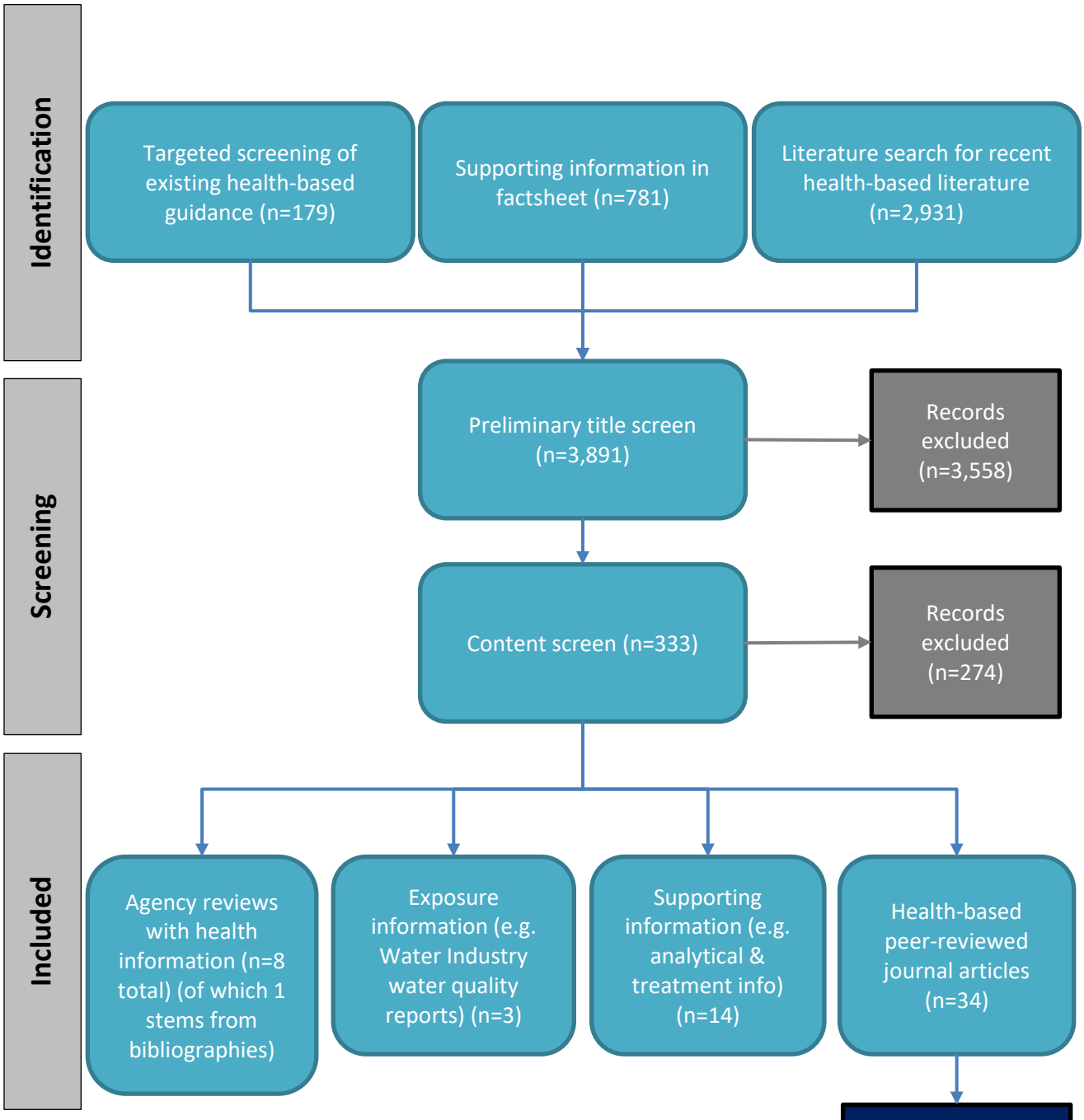
#	Research Questions
3	If there are existing guidance/guideline values, is the proposed option for a health-based guideline value relevant to the Australian context?
4	Is there a knowledge gap from the time at which existing guideline values were developed?
5	Does any recent literature change the proposed guideline value (e.g. demonstrating a new critical endpoint or changed level of effect that should be considered)?
6	What are the key adverse health hazards from exposure to silicon in Australian drinking water?
7	Are there studies quantifying the health burden (reduction or increase) due to silicon?
8	What is the critical human health endpoint for silicon?
9	What are the justifications for choosing this endpoint?
Exposure Profile	
10	What are the typical silicon levels in Australian water supplies? Do they vary around the country or under certain conditions e.g. drought?
11	Are there any data for silicon levels leaching into water from in-premise plumbing?
Risk Summary	
12	What are the risks to human health from exposure to silicon in Australian drinking water?
13	Is there evidence of any emerging risks that require review or further research?
Supporting Information on Factsheet	
14	What is silicon used for and how might people be exposed?
15	How is the concentration of silicon measured in drinking water?
16	What are the indicators of the risks? How can we measure exposure?
17	What analytical methods are currently used to measure silicon in drinking water?
18	What are the limits of quantification or limit of reporting for silicon in drinking water?
19	How is drinking water treated to minimise silicon concentrations?
20	What are the current practices to minimise or manage the risks identified?

3 Evidence Evaluation Methods

3.1 Overview

This section summarises the methods followed to undertake the evidence evaluation review for silicon. The intention is to provide enough detail for a third party to reproduce the search.

It was evident that some flexibility was required in adapting the methodology recorded in the final Research Protocol for silicon to maximise efficiency in sourcing relevant information. Deviations from the final Research Protocol methodology have been recorded in this report. **Figure 1** shows an overview of the literature search process followed for silicon. This is presented as a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram that describes the study selection process and numbers of records at each stage of screening (Moher et al. 2009).



*Risk of bias assessments were not undertaken for studies that were excluded from further assessment due to being reviews (which were used to identify additional individual studies) or due to providing only very limited or no dose response information for potential guidance/guideline value development.

Figure 1 Overview of literature search process followed for silicon

3.2 Targeted screening of existing health-based guidance

Literature search strategy

The literature search strategy for existing health-based guidance documentation for silicon is summarised in **Table 2** below.

Table 2 Search strategy for Existing Guidance/Guidelines

Parameter	Comments
Search terms	After a few trial runs of various combinations of search terms, it became apparent that the search terms would need to remain relatively broad so as not to miss pivotal references/reviews. Consequently, the selected search term was: • (silicon)
Databases/Agency websites	The following sources were searched: • World Health Organization (WHO): https://www.who.int/ • International Programme of Chemical Safety (IPCS Inchem): http://www.inchem.org/#/search • Joint FAO/WHO Expert Committee on Food Additives (JECFA): (Included in IPCS Inchem search) • European Food Safety Authority (EFSA): https://www.efsa.europa.eu/en • United States Environmental Protection Agency (US EPA) (1): • US Agency for Toxic Substances and Disease Registry (ATSDR): https://www.atsdr.cdc.gov/ • Californian Office of Environmental Health and Hazard Assessment (OEHHA) Public Health Goals (in Drinking Water): https://oehha.ca.gov/water/public-health-goals-phgs • Food Standards Australia New Zealand (FSANZ) • Australian Pesticides and Veterinary Medicines Authority (APVMA) Health Based Guidance Values: https://apvma.gov.au/node/26596 The following additional sources were searched to provide exposure information in Australian drinking water supplies (to inform responses to Research Questions 10 and 11): • Melbourne Water: https://www.melbournewater.com.au/ • Sydney Water: https://www.sydneywater.com.au/SW/index.htm • TasWater: https://www.taswater.com.au/ • SA Water: https://www.sawater.com.au/ • Water Corporation of Western Australia: https://www.watercorporation.com.au/ • Power and Water Corporation Northern Territory Drinking Water Quality Reports: https://www.powerwater.com.au/about/what-we-do/water-supply/drinking-water-quality/past-drinking-water-quality-reports • Seqwater: https://www.seqwater.com.au/ • Icon Water: https://www.iconwater.com.au/ • Water Research Australia: https://www.waterra.com.au/
Publication Date	No cutoff date (all dates included)
Language	English

Parameter	Comments
Study Type	• Publicly available agency/industry reports and reviews of guidelines or evidence supporting guidelines (near publication drafts are included if available). • Published water quality datasets.

Inclusion and exclusion criteria	The following exclusion criteria were used to screen relevance of agency reports/reviews:
	• NR = Not Relevant. Information not directly relevant to answering research questions. Rationale for non-relevance was provided for transparency. E.g.
	  ○ Not HH related = Not human health related (e.g. criteria are for protection of aquatic life).
	  ○ Not a relevant exposure pathway = Since silicon is not volatile, guidelines for non-oral and non-dermal routes of exposure are not considered relevant (e.g. inhalation). For example, the health effects related to exposure to silicon dioxide (SiO_2) in dust are very different from those that would be associated with ingestion of silicon.
	  ○ Not relevant to substance of interest.
	• NPA = Basis of guideline value or information underpinning review conclusions are Not Publicly Available, e.g. health-based guideline value has used unpublished proprietary information which could not be verified.
	• L = Language other than English.
	• Inhalation studies with silica (i.e. silicon dioxide) were excluded, as the adverse effects from inhalation are well-known and very different from those due to oral exposure to silica/silicates.
	• Studies specifically testing the toxicity of silica nanoparticles or nanomaterials were excluded during the content screen. These were not deemed to be relevant to the exposure circumstances of interest, i.e. oral exposure from potential leaching of silicon from silicon brasses.[2]

Validation methods used	Preliminary searches were undertaken with more specific search terms [(Silicon) AND (toxicity or health) AND (oral); (Silicon) AND (health) AND (oral)]. Upon scanning preliminary search results, the reviewer found these search terms to be too specific, as very low or no agency reports appeared in the results. The search terms were consequently refined (see **Appendix A**).
Screening methods	Results were screened as follows: *Preliminary title screen* • Titles of results for each search were recorded in an Excel spreadsheet. • The researcher scanned the titles. In a separate column a decision regarding relevance of the result was recorded as per the exclusion criteria. An additional column was included to provide commentary as (and if) required. • Where the researcher was uncertain as to the relevance of a particular result, the researcher discussed the matter with a subject expert prior to making a decision OR the result was considered potentially relevant and included. *Content screen* • The full text content of reports/reviews selected to be included from the preliminary title screen were reviewed by a subject expert to determine which reports/reviews to include in the data extraction step. Only reports/reviews which provided information relevant to answering the research questions were taken through to the data extraction step. • Articles related to nanoparticles were included/excluded in this screen.

Parameter	Comments
Documentation of search	Spreadsheets with full search results and screening outcomes (i.e. reasons for exclusion) are provided in **Appendix A.** Overall results presented in **Figure 1**, adapted from the PRISMA figure presented in Moher et al. (2009) and Figure 5 in OHAT (2019).
Retrieval of publications	All relevant and potentially relevant results were recorded in an Endnote library and soft copies of files saved into a designated folder on the SLR server for review. The server is backed up on a daily basis.

1. The search within the US EPA general search engine (https://www.epa.gov/) resulted in 13,675 hits, regardless of search term refinement. This number of hits was considered unmanageable to screen with the resources available for this project, especially considering search results became increasingly less relevant. Consequently, the search was cut off after the first 10 results (subsequent search results were considered irrelevant to answering the research questions).
2. There were a few instances where data from synthetic amorphous silica (SAS) was also included, where particles are technically in the nanometre size range but agglomerate to >100 nm in size prior to administration to experimental animals. It is, however, uncertain, how relevant these data are for the exposure circumstances considered in this report.

Data Collection and Quality Assessment

For each relevant result for which the full text was sourced:

- The full text was screened by a content expert.
- Where existing health-based guidance (in the form of drinking water guidelines or toxicity reference values, i.e. TRVs) was identified, relevant data on the guidance value in relation to the research questions were collected using the format shown in **Table 3.** The individual data collection tables are provided in **Appendix B**. Although several reviews were identified in the targeted search, only one (EVM 2003) (identified through consulting bibliographic citations in other reviews) provided a health-based guidance value.
- As per the guidance in the Research Protocol, quality of the existing guidance/guideline (EVM 2003) was assessed using the Assessment Tool in the Research Protocol.

Table 3 Example of data extraction table format for existing health-based guidance

Agency Report Reference: *Insert full bibliographical reference for report*		
General Information	Date of data extraction	
	Authors	
	Publication date	
	Literature search timeframe	
	Publication type	
	Peer reviewed?	
	Country of origin	
	Source of funding	
	Possible conflicts of interest	
Health considerations	Guideline value type (e.g. oral TRV, drinking water guideline)	
	Exposure timeframe	

Agency Report Reference: *Insert full bibliographical reference for report*		
	Critical human health endpoint	
	Justification provided by agency for critical endpoint	
	Critical study(ies) underpinning point of departure	
	Species for critical study(ies)	
	Point of departure type (e.g. NOAEL, LOAEL, $BMDL_{10}$, etc)	
	Point of departure value (include units)	
	Uncertainty factor(s) & rationale	
	Guideline value (include units)	
	Mode of action for critical health endpoint	
	Genotoxic carcinogen?	
	Identified sensitive sub-populations	
	Any non-health based considerations?	
Exposure considerations	Principal routes of exposure in general population	
	Levels in drinking water supplies (include location)	
	Any special considerations to exposure levels (e.g. higher in drought?)	
	Typical exposure in general population (include units for intakes & location)	
Risk Summary	Any risks to human health from drinking water identified in agency document?	
	Any emerging risks identified?	

Data summary/synthesis

The data from the various existing health-based guidance/guideline value reviews was summarised in tabular format for each individual research question.

Expert judgement was used to highlight and record areas of uncertainty or areas where an organisation's methods/interpretation differs from Australian science policy.

3.3 Detailed full evidence review of health-related studies

Literature search strategy

An additional literature search was undertaken in two scientific databases for published studies relevant to addressing the health-related research questions. A full review of the literature was undertaken (as opposed to simply undertaking an evidence scan for any recent health-based information that could impact the guidance/guideline value).

The literature search strategy for undertaking the full review in scientific databases is summarised in **Table 4** below.

Table 4 Search strategy for full review of health-based studies

Parameter	Comments
Search terms	The selected search terms were: • (Silicon) AND (toxicity) AND (oral) • (Silicon) AND (health) AND (oral) • (Silicon) AND (drinking water) • (Silicon) AND (plumbing) AND (leaching)
Databases	The following sources were searched: • MEDLINE/PubMed/TOXLINE • SciFinder
Publication Date	As there is no existing fact sheet for silicon, the search did not have a minimum cutoff date. Dates at which searches were conducted are recorded in individual spreadsheets in **Appendix A**.
Language	English
Study Type	Peer-reviewed published, in press, unpublished (but publicly available) and ongoing studies were included. Study types may include existing systematic reviews or literature reviews, human epidemiological studies, or animal studies (where there was insufficient human information). *In vitro* studies were not included.
Inclusion and exclusion criteria	The following exclusion criteria were used to screen relevance of information: • NR = Not Relevant. Information not directly relevant to answering research questions. • Provides little or no useful information about substance of interest (silicon). • Language = Language other than English.
Validation methods used	Preliminary test searches were undertaken to assist with selecting search terms. Refinements were made as considered appropriate to ensure adequate, but also specific coverage in the sources screened (see **Appendix A**).

Parameter	Comments
Screening methods	Results were screened as follows: *Preliminary title and abstract screen* • Titles of results for each search were recorded in an Excel spreadsheet. The results for each combination of search terms were exported into a separate tab of the spreadsheet. To readily eliminate duplicate records, results from all search term combinations were subsequently collated into one spreadsheet. • The researcher scanned the titles (and abstracts, if required). In a separate column a decision regarding relevance of the result was recorded as per the exclusion criteria. An additional column was included to provide commentary as (and if) required. • Where the researcher was uncertain as to the relevance of a particular result, the researcher discussed the matter with a subject expert prior to making a decision OR the result was considered potentially relevant and included. *Content screen* • The full text content of literature selected to be included from the preliminary title and abstract screen were reviewed by a subject expert to determine which articles to include in the data collection and analysis step. *Additional search of relevant bibliographies* In addition to the primary search, the bibliographies of critical review papers were consulted to source additional papers of potential relevance. The latter papers were only subjected to the content screen.
Documentation of search	Spreadsheets with full search results and screening outcomes (i.e. reasons for exclusion) are provided in **Appendix A.** Overall results presented in **Figure 1**, adapted from the PRISMA figure presented in Moher et al. (2009) and Figure 5 in OHAT (2019).
Retrieval of publications	All relevant and potentially relevant results were recorded in an Endnote library and soft copies of files saved into a designated folder on the SLR server for review. The server is backed up on a daily basis.

Data Collection

For each relevant result for which the full text was sourced:

- Where deemed to be relevant to the research questions, relevant data were extracted using the example format shown in **Table 5.** The format was more applicable to epidemiological studies and was adapted slightly for animal studies and/or reviews. The individual data extraction tables are provided in **Appendix C**.

Table 5 Example of data collection table format for full review of health-based studies

Publication Reference: ***Insert full bibliographical reference for report***		
General Information	Date of data extraction	
	Authors	
	Publication date	
	Publication type	
	Peer reviewed?	

Publication Reference: ***Insert full bibliographical reference for report***		
	Country of origin	
	Source of funding	
	Possible conflicts of interest	
Study characteristics	Aim/objectives of study	
	Study type/design	
	Study duration	
	Type of water source (if applicable)	
Population characteristics	Population/s studied	
	Selection criteria for population (if applicable)	
	Subgroups reported	
	Size of study	
Exposure and setting	Type of water source (if applicable)	
	Exposure pathway	
	Source of chemical/contamination	
	Exposure concentrations (if applicable)	
	Comparison group(s)	
Study methods	Water quality measurement used	
	Water sampling methods (monitoring, surrogates)	
Results (for each outcome)	Definition of outcome	
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	
Statistics (if any)	Statistical method used	
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	
Author's conclusions	Interpretation of results	
	Assessment of uncertainty (if any)	

Publication Reference: ***Insert full bibliographical reference for report***		
Reviewer comments	Results included/excluded in review (if applicable)	
	Notes on study quality, e.g. gaps, methods	

Data analysis

All critical studies deemed relevant for defining the dose response of silicon were subjected to a risk of bias (RoB) assessment with the use of a RoB tool (i.e. modified OHAT tool, shown in **Table 6**)[1]. The justification for excluding some studies from RoB assessments can be found in the individual data extraction summary tables in **Appendix C.** Outcomes of these assessments are provided as a rating for each parameter; individual assessments are provided in **Appendix D**.

[1] The example of the modified OHAT tool provided in this section is for a case study report. The table was amended to include fields deemed applicable to other study types.

Table 6 Modified OHAT risk of bias tool (example: case study report) adapted from OHAT, 2019

Study ID: **Study Type:**		**RoB:** **Yes/No, Unknown, N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	N/A	Comparison groups: not applicable	
	Confounding bias			
4.	Confounding (design/analysis)			
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	N/A	Missing outcome data: not applicable	
	Detection Bias			
8.	Exposure characterisation			
9.	Outcome assessment			
	Selective Reporting Bias			
10.	Outcome reporting			
	Other Sources of Bias			
11.	Other threats	N/A		

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Relevant data were summarised in tabular format by research question, and by study design. Where possible, synthesis was conducted by presenting combined data for the same health outcome. Due to resource constraints and data limitations, meta-analysis of the study findings was not undertaken.

Summary tables were constructed for the following:

- Threshold doses of silicon associated with no adverse effects and critical adverse health effects, where possible.
- RoB assessments across the body of evidence for each evidence stream and health outcome.
- Overall certainty of evidence for different health endpoints by study design. This considered the overall confidence of the body of evidence with regard to RoB, indirectness/applicability, imprecision, inconsistency between studies and publication bias, with information provided as a certainty rating where possible using guidance from OHAT (2019). Note hazard identification conclusions were not developed.

These aspects are presented in the Evidence Evaluation Report.

3.4 Supporting information in factsheet

In the first instance, the existing guidance/guideline documents identified as per the methods outlined in **Section 3.2** were consulted for supporting information in the factsheet (i.e. general description, uses, measurement techniques and limits of reporting in drinking water, treatment options, etc).

The information was collated into data extraction tables such as the one in **Table 7**. The individual data extraction tables for supporting information are provided in **Appendix E**.

Table 7 Example of data extraction table format for supporting information in factsheet

Agency Report Reference: ***Insert full bibliographical reference for report***		
General Description	Uses	
	Sources in drinking water	
	Other	
Treatment of drinking water	Treatment technology	
	Effectiveness	
	Any special conditions?	
	Other	
Measurement	Analytical method	
	Limit of determination/ Limit of Reporting (LOR)	
	Other	
Additional information	Any additional non-health related information considered important?	

In addition, a literature search of recent publicly available information was undertaken as per the methodology shown in **Table 8** below.

Table 8 Search strategy for supporting information in factsheet

Parameter	Comments
Search terms	The selected search terms were: • (Silicon) AND (treatment) AND (drinking water) • (Silicon) AND (analysis) AND (drinking water) • (Silicon) AND (testing) AND (drinking water) After a few trial runs of various combinations of search terms in the industry websites, it became apparent that the search capacities varied markedly between different webpages. Consequently, the selected search term (for industry websites) was kept relatively broad: • (Silicon)
Databases/Other sources	The following databases were searched: • Medline/PubMed/Toxline • Scopus The following industry websites were searched: • Water Services Association of Australia: https://www.wsaa.asn.au/ • Standard Methods for the Examination of Water and Wastewater: https://www.standardmethods.org/ • US EPA Drinking Water Treatability Database: https://tdb.epa.gov/tdb/home The following Australian commercial laboratories were contacted directly via e-mail or website form for relevant information: • National Measurement Institute • SGS • ALS • Eurofins
Publication Date	The search was conducted from 2008 to the present date. This covers the last 15 years of information and is considered appropriate for supporting information, as older information may be considered to be outdated (especially in terms of treatment and analytical methods).
Language	English
Study Type	• Peer-reviewed, published or in-press studies. • Unpublished studies (e.g. government reports). • Australian laboratory information sheets or e-mail responses on measurement methods and limits of determination.
Inclusion and exclusion criteria	The following exclusion criteria were used to screen relevance of information: • NR = Not Relevant. Information not directly relevant to answering the research questions. • Research technique (analytical or treatment) = does not appear to be applied commercially. • Language = Language other than English. • NPA = Not publicly available. • NL = Chemical not listed under specific treatment process.

Parameter	Comments
Validation methods used	Preliminary test searches were undertaken to assist with selecting search terms. Refinements were made as considered appropriate to ensure adequate, but also specific coverage in the sources screened (see **Appendix A**).
Screening methods	Results were screened as follows: *Preliminary title and abstract screen* • Titles of results for each search were recorded in an Excel spreadsheet. Each source was on a separate tab of the spreadsheet. These were collated into a single spreadsheet, excluding duplicates. • The researcher scanned the titles (and abstracts, if required). In a separate column a decision regarding relevance of the result was recorded as per the exclusion criteria. An additional column was included to provide commentary as (and if) required. • Where the researcher was uncertain as to the relevance of a particular result, the researcher discussed the matter with a subject expert prior to making a decision OR the result was considered potentially relevant and included. *Content screen* • The full text content of literature selected to be included from the preliminary title and abstract screen were reviewed by a subject expert to determine which articles to include in the data extraction step. Only articles/reviews which provided information relevant to answering the research questions were taken through to the data extraction step.
Documentation of search	Spreadsheets with full search results and screening outcomes (i.e. reasons for exclusion) are provided in **Appendix A.** Overall results are presented in **Figure 1**, adapted from the PRISMA figure presented in Moher et al. (2009) and Figure 5 in OHAT (2019).
Retrieval of publications	All relevant and potentially relevant results were recorded in an Endnote library and soft copies of files saved into a designated folder on the SLR server for review. The server is backed up on a daily basis.

The following data were extracted from relevant publications and/or obtained from correspondence with Australian laboratories:

- Citation information
- Name of treatment technology (as applicable)
- Name of analytical technique (as applicable)
- Associated Reporting Limit

The individual data extraction tables for supporting information are provided in **Appendix E**.

4 Results

A summary of the responses to the research questions for silicon is provided in the tables below.

One existing health-based guidance value was found in the literature retrieved (i.e. EVM 2003, as identified by consulting the bibliographies of health-based literature), but additional agency reviews were identified from the agency literature search (note none of these related to silicon in drinking water). Responses to research questions are based on these agency reviews and data extractions conducted for the various experimental animal (EA) studies, cross-sectional (CrSe), cohort (Co) and a human controlled trial (HCT) found in the primary literature reviewed.

4.1 Health-based research question analysis

Table 9 Synthesis of extracted data for health-based research questions

#	Research Questions	Publications	Response to Research Questions
1	What level of silicon in drinking water causes adverse health effects?	Various	No existing health-based drinking water guideline values were found in the literature searched according to the Research Protocol. However, EVM (2003) derived an oral guidance value of 25 mg/kg bw/day supplemental silica (equivalent to 12 mg/kg bw/d elemental silicon) from chronic / carcinogenicity studies in rats and mice in which no treatment-related adverse effects were observed at the highest dose of amorphous silica administered via the diet (i.e. 2,500 mg/kg bw/day in rats; 7,500 mg/kg bw/d in mice) (Takizawa et al. 1988). It is noted, however, that EFSA (2004) commented that extrapolation of these data to other forms of silicon (such as silicates) is inappropriate but later EFSA (2009, 2018a) used the guidance value from EVM (2003) in an evaluation of the safety of various silicates (calcium silicate, silicon dioxide, silicic acid gel, orthosilicic acid-vanillin) as silicon sources in food. In humans, apart from occasional reports of renal stones, mainly associated with long-term use of silicate-containing antacids (e.g. as magnesium trisilicate), there is little evidence of adverse effects of orally ingested silicon (EFSA 2010, FAO/WHO 1974). Indeed, available epidemiological information (albeit limited) and some animal studies suggests a potential protective effect of silicon in drinking water (Burton et al. 1980, Gillette-Guyonnet et al. 2007, Jacqmin-Gadda et al. 1996, Najda et al. 1991). Experimental studies in rats conducted over a 4-week period with different forms of silica in the diet found no adverse effects from administration of ~370 mg Si/kg bw/d when administered as silicon dioxide, aluminium silicate, sodium silicate or magnesium trisilicate; however, in dogs this dose of silicon when administered as sodium silicate or magnesium trisilicate resulted in renal lesions (Newberne and Wilson 1970). Renal effects have also been reported in guinea pigs exposed orally to 16-32 mg Si/kg bw/d as magnesium trisilicate in drinking water for 5 days/week for 4 months, but not when administered as crushed quartz or crushed granite (Dobbie and Smith 1982). EFSA (2018c) commented that kidney effects observed in dogs were most probably related to the large amount of test compound consumed as a bolus dose by the animals. Newberne and Wilson (1970) state dogs were administered the test compound in a highly palatable diet. It is not completely clear from the study whether this was done by bolus capsule along with a palatable diet or mixed into the diet; according to EFSA (2018c) administration occurred via bolus dosing. SLR has relied partially on the EFSA (2018c) interpretation of this study. The effects on the kidney reported in guinea pigs could be due to higher concentrations of silicate in the primary urine because of lower glomerular filtration rates in guinea pigs (2.29 mL plasma/min per kg) compared to rats (4.63 mL plasma/min per kg). EFSA (2018c) noted that in humans the glomerular filtration rate (3.56 mL plasma/min per kg) is higher than in guinea pigs and kidney effects (apart from stones) have not been found in humans despite the wide and long-term use of high doses of magnesium trisilicate (up to 4 g/person per day) as an antacid over decades. Other toxicological studies conducted in rats with micronised synthetic amorphous silica (SAS) have found no treatment-related adverse effects in these animals (e.g. Lewinson et al. 1994, Wolterbeek et al. 2015, Yoo et al. 2022, Liang et al. 2018).

#	Research Questions	Publications	Response to Research Questions
2	What is the endpoint that determines this value?	Takizawa et al. 1988; EVM 2003; Dobbie and Smith 1982; Newberne and Wilson 1970; Gloxhuber et al. 1983; Markovic and Arambasic 1971	No treatment-related adverse effects observed in dietary chronic / carcinogenicity studies in rats/mice. It is, however, noted that in dogs and guinea pigs, when administered in the diet or drinking water as magnesium trisilicate or sodium silicate or pure quartz suspension for 1-4 months, histopathological lesions in the kidney were observed.
3	If there are existing guidance/guideline values, is the proposed option for a health-based guideline value relevant to the Australian context?	EVM 2003; EFSA 2004, 2009	The available guidance value from EVM (2003) is likely relevant to the Australian context for dietary exposures to food-grade amorphous silica. However, EFSA (2004) commented that the extrapolation of these data to other forms of silicon (such as silicates) is inappropriate, whereas EFSA (2009, 2018a) later used the guidance value from EVM (2003) in evaluations of the safety of various silicates (calcium silicate, silicon dioxide, silicic acid gel, orthosilicic acid-vanillin complex) as sources of silicon in food. It is unknown what form silicon from silicon brasses will likely be if it were to leach from lead-replacement plumbing, but it is most likely to be in the form of solubilised silicon (e.g. orthosilicic acid); if this is assumed to be correct, the EVM (2003) guidance value is likely relevant to the Australian context.
4	Is there a knowledge gap from the time at which existing guideline values were developed?	Various	A detailed literature review was undertaken for health-based information for silicon. The literature search identified numerous additional studies however the majority of the critical information was already available to EVM (2003) at the time the guidance value was derived. Thus, the additional information would be unlikely to alter the assessment done by EVM (2003).
5	Does any recent literature change the proposed guideline value (e.g. demonstrating a new critical endpoint or changed level of effect that should be considered)?	Not applicable	See Response to Research Question 4.

#	Research Questions	Publications	Response to Research Questions
6	What are the key adverse health hazards from exposure to silicon in Australian drinking water?	**Agency reports: EFSA 2004, 2009, 2010, 2018a, 2018c; EVM 2003, FAO/WHO 1969, 1974**	In humans, apart from occasional reports of renal stones, mainly associated with long-term use of silicate-containing antacids (e.g. as magnesium trisilicate), there is little evidence of adverse effects of orally ingested silicon (EFSA 2010, FAO/WHO 1974, EFSA 2018c). EFSA (2018c) also indicates the occurrence of urinary silicate calculi is seldom (0.1-0.2% of all urinary stones) and the association between silicate antacid use and renal calculi is 'possible' but not 'definite', which means it cannot be excluded that the occurrence of renal calculi and intake of silicates is a chance finding. Experimental studies in rats have also found no treatment-related adverse effects from dietary administration of various silicon compounds, whereas one study in dogs (diet bolus dose) and one in guinea pigs (drinking water) found renal histopathological findings when animals were administered sodium silicate or magnesium trisilicate (but not silicon dioxide or aluminium silicate).
		EA (drinking water): Austin 1978	No adverse effects observed in mice (n=27), rabbits (n=3), monkey (n=1) or dog (n=1) given drinking water containing 50 and 1,000 mg Si/L as soluble silicon ($Na_2SiO_3.9H_2O$) for 4 months.
		EA (drinking water): Markovic and Arambasic 1971	Chronic interstitial nephritis observed in guinea pigs (number not reported) given tap water containing a quartz suspension (50 or 250 mg/L, dose not reported) for up to 6 months. Quartz was sourced from a region in Yugoslavia known to be prone to endemic nephropathy in humans.
		EA (drinking water): Dobbie and Smith 1982	Focal tubule-interstitial nephritis in 6/6 guinea pigs given tap water containing magnesium trisilicate (7.5 mg/L, i.e. 16-32 mg Si/kg/d) for 4 months. Similar but less intense lesions were encountered in two animals (2/6) receiving crushed quartz. No renal lesions were found in control group or in animals receiving crushed granite.
		EA (drinking water + feed): Jugdaohsingh et al. 2008, 2015a	No adverse effects in rats from total dose of soluble Si (from feed and water) of 4.08 ± 0.74 mg/kg/d in the supplemented group and perhaps 18.51 ± 0.65 mg/kg/d in the referent group after 26 weeks of exposure (Jugdaohsingh et al. 2008); or up to 57.4 mg/kg/d in mice (from feed and water) after 15-19 weeks of exposure (only limited endpoints examined) (Jugdaohsingh et al. 2015a). There is uncertainty regarding the lack of adverse effects at 18.51 ± 0.65 mg/kg/d in the referent group in the first study (Jugdaohsingh et al. 2008), since due to other nutritional differences, the two diets were not compared in this study with regards to the effect of silicon on the rats. Rats on the standard rodent stock feed served only as a reference for normal anthropogenic measures. Nevertheless, no mention of adverse effects in the control group was made in the paper.
		EA (drinking water): Najda et al. 1991	Suggests beneficial effect of silicon in drinking water given to rats (100-400 mg Si/kg bw/d) for progressive 6-week periods. Very limited parameters investigated.

#	Research Questions	Publications	Response to Research Questions
		EA (diet): Newberne and Wilson 1970	No adverse effects in rats from 4-week administration of ~370 mg Si/kg bw/d when given as silicon dioxide, aluminium silicate, sodium silicate or magnesium trisilicate in the diet; however, in dogs this dose of silicon when administered as sodium silicate or magnesium trisilicate in the diet resulted in renal lesions.
		EA (diet): Takizawa et al. 1988	No adverse effects in rats given 1.25-5% SYLOID (food grade micronized silica) in diet to rats or mice for ~2 years. Based on the doses reported by EVM (2003), this study provides NOAELs of 2,500 mg Si/kg/d in rats and 3,500 mg Si/kg/d in mice (top dose tested).
		EA (diet): Gloxhuber et al. 1983	No treatment-related adverse effects in rats given up to 1,000 ppm Zeolithe A (an aluminosilicate) in the diet for 2 years. This corresponds to a dose of 58.47 mg/kg/d in males and 62.15 mg/kg/d in females. Si content, based on molecular formula is ~15%, which suggests a chronic NOAEL of 8.8 mg/kg/d in males and 9.3 mg/kg/d in females for the Si content in Zeolithe A may be applicable.
		EA (gavage or diet): Lewinson et al. 1994	Standard toxicological package for oral acute, subacute, chronic and carcinogenicity studies with hydrophobic amorphous nanosilicas (may not be entirely relevant to silica subject of this report) found no adverse effects in any studies where administration was via diet or gavage (lowest NOAEL was highest dose tested in 24-month carcinogenicity study of 100 mg/kg/d).
		EA (gavage): Liang et al. 2018	No adverse effects in rats given up to 1,500 mg/kg/d silica microparticles for 90 days by oral gavage.
		EA (gavage): Wolterbeek et al. 2015	No adverse effects in 2-generation toxicity study in rats administered synthetic amorphous silica (SAS) by oral gavage (NOAEL was top dose tested = 1,000 mg/kg/d). Note SAS is a nanostructured material and a form of SiO_2, with aggregates having external dimensions typically above 100 nm.
		EA (gavage): Yoo et al. 2022	No adverse effects in 28-day toxicity study with rats administered food grade SAS and precipitated SAS up to top doses tested (2,000 mg/kg/d) via oral gavage.
		Prospective cohort: Rondeau et al. 2009	Large prospective cohort study (15-year follow-up) found no association for silica exposure in drinking water or bottled water (up to a concentration of 22.4 mg/L in tap water, 77.6 mg/L in bottled water) and cognitive decline, dementia, and Alzheimer's disease in France.
		CrSe: Burton et al. 1980	For Si concentrations 0 to 15 mg/L in drinking water, there was a significant regression and negative correlation with age-adjusted death rate from cancer in the USA. For the rest of the range of concentrations (15-70 mg/L) there was no further significant reduction in death rates.
		CrSe: Jacqmin-Gadda et al. 1996	No significant association between silica concentration (4.2-22.4 mg/L) in drinking water and cognitive impairment, suggested a protective effect of silica against aluminium from drinking water.

#	Research Questions	Publications	Response to Research Questions
		Observational study: Gitelman et al. 1992	Exposure to silicon in dialysis fluids (1.9-5.2 mg/L) can increase silicon levels in plasma. No overt adverse health effects from silicon exposure in dialysis fluid in end-stage renal disease but study limited by the limited endpoints examined.
		Observational study: Mascarenhas et al. 2017	Study authors make a large claim in terms of silica exposure in groundwater (at 115.5 mg/L but not at ~13.5 mg/L) being the potential cause for chronic kidney disease observed in some villages in India. However, no statistical analysis or odds ratios were calculated in this study and no correction for confounders was undertaken. The authors used the results of *in vitro* cytotoxicity assays to argue for such an association.
		Ecological study: Rapant et al. 2015	Study authors concluded that SiO_2 in drinking water (18.21 mg/L) is unlikely to be causally related to relative mortality for cardiovascular disease (RelI) even though a statistical relationship between the two factors was observed.
		HCT: Hagman et al. 2020	Although a limited number of endpoints were monitored, this study suggests that an oral dose of 110 mg Si/kg bw/d (as mesoporous silica) for 16 days (excluding placebo period) in healthy weight individuals and 80 mg Si/kg bw/d for ~12 weeks does not result in any overt adverse health effects in male humans.
		Review: Elmore et al. 2003	• No adverse effects in rats fed synthetic zeolite A (aluminosilicate) in the diet for 2 years (top dose 58.5 mg/kg/d in males, 62.2 mg/kg/d in females). • No adverse effects in pregnant rabbits or offspring given calcium silicate via gavage at 1,600 mg/kg (top dose) for 13 consecutive days. • No teratogenic effects in pregnant mice or offspring given magnesium aluminium silicate by gavage up to 6,000 mg/kg/d on gestation day 7-12. • No adverse effects in pregnant rats or rabbits (or their offspring) given Type A zeolite containing 19% silicon by gavage at 1600 mg/kg/d during pregnancy.
		Review: Willhite et al. 2012	Review focused on toxicity of aluminium but included consideration of aluminium silicates. Although this provides little information with respect to toxicity of silicon *per se*, it provides support that silicon in montmorillonite clays is of relatively low toxicity. It describes a 90-day randomized, double-blind, placebo-controlled Phase II clinical trial with dietary calcium montmorillonite (Novasil clay) administered in capsules to 180 healthy male and female volunteers at 0, 20, or 40 mg/kg/d with no adverse effects observed. Silicon content in this clay is not provided.

#	Research Questions	Publications	Response to Research Questions
7	Are there studies quantifying the health burden (reduction or increase) due to silicon?	**Burton et al. 1980, Gilette-Guyonnet et al. 2007, Jacqmin-Gadda et al. 1996**	See response to Research Question 6. Available epidemiological information (albeit limited) suggest a potential protective effect of silicon in drinking water.
8	What is the critical human health endpoint for silicon?	**Most publications**	Most publications have not identified any adverse effects from exposure to silicon in humans, rats, mice, and rabbits. In humans, according to EFSA (2010) and FAO/WHO (1974) apart from occasional reports of renal stones, mainly associated with long-term use of silicate-containing antacids (e.g. as magnesium trisilicate), there is little evidence of adverse effects of orally ingested silicon. EFSA (2018c) also indicates the occurrence of urinary silicate calculi in humans is seldom (0.1-0.2% of all urinary stones) and the association between silicate antacid use and renal calculi is 'possible' but not 'definite', which means it cannot be excluded that the occurrence of renal calculi and intake of silicates is a chance finding.
		EA: Dobbie and Smith 1982, Newberne and Wilson 1970, Markovic and Arambasic 1971	In one study with dogs and another two with guinea pigs, histopathological renal lesions were identified after administration of some forms of silicates (sodium and magnesium silicate in one study; quartz suspension in another study). This may be the critical health endpoint for silicon exposure, but from the available information humans appear to be markedly less sensitive to these effects compared to dogs or guinea pigs.
9	What are the justifications for choosing this endpoint?	As above	As above.

4.2 Exposure-related research question analysis

Table 10 Synthesis of extracted data for exposure-related research questions

#	Research Questions	Publications	Response to Research Questions
10	What are the typical silicon levels in Australian water supplies? Do they vary around the country or under certain conditions e.g. drought?	**Water corporations: Melbourne Water 2021, PWNT 2020, WCWA 2020**	Victoria: • 2.3 to 7.2 mg/L Northern Territory: • Mean values as SiO_2 11 to 104 mg/L (i.e. 5.2 to 49 mg Si/L) Western Australia: • Mean values 0.6 to 90 mg/L
		Dayanand et al. 2019	In India: • Reverse osmosis (RO) water: 2.8 mg/L • Bore water in mining area: 62-68 mg/L
		Dobbie and Smith 1986	Differed depending on region of United Kingdom (UK) and water treatment used: • Low tap water Si: 0.4 mg/L • Intermediate tap water Si: 2.2 mg/L • Intermediate tap water Si, with reverse osmosis: 0.95 mg/L • High tap water Si: 4 mg/L
		Benson et al. 2017	In source and treated drinking water from 25 drinking water treatment plants across the USA sampled in 2010-2012, silicon was detected in every sample (maximum = 22.26 mg/L)
		Desai et al. 2012	In Ahmedabad, India concentrations in groundwater (used for drinking) ranged from 18.2 to 53.9 mg Si/L.
		Ghaffari et al. 2021	In tap drinking water and filtration plants in Bandar Abbas city in Iran (March-July 2020): • Mean ± SD concentration of Si in tap water was 6,356.25 ± 1282 µg/L (i.e. 6.3 mg/L) • In filtration plants it was 1825 ± 748 µg/L (i.e. 1.8 mg/L).
		Morykwas et al. 1991	Concentrations of Si in water purification facilities for a number of different cities in USA range from 0.32 to 33 mg/L, with means ranging from 0.68 to 17.3 mg/L.

#	Research Questions	Publications	Response to Research Questions
		NRC 1979	The maximum, median, and minimum concentrations of silicon as silica in finished water from water supplies of the 100 largest cities of the USA were 72, 7.1 and 0 mg/L respectively; no mean concentrations were given. Natural waters may contain from a few to several thousand mg Si/L.
		Powell et al. 2005	In UK, tap water samples (n=4) contained a mean of 2.5 mg Si/L.
		Rauf et al. 2021	Concentrations of SiO_2 in 14 well water samples collected around the residential area near cement industrial activity and karst mining in Indonesia. • Mean SiO_2 concentration was 12.94 mg/L (range 7.4 – 20.9 mg/L).
		Vertrimurugan et al. 2017	Groundwater (n=40) in intensively irrigated part of the Cauvery River basin, Tamil Nadu, India in January 2015 contained Si ranging from <LOR (LOR not reported) to 26.48 mg/L (mean = 9.82 mg/L).
		Rawat et al. 2020	Silica present at 15.5 – 24 mg/L according to the data collected from the Central Groundwater Board-Chennai, India.
11	Are there any data for silicon levels leaching into water from in-premise plumbing?	**Choucri et al. 2021**	Silicon brasses with various compositions were developed to induce grain refining and strength increase or to produce non-toxic lead- and arsenic-free alloys with good machinability and dezincification resistance. CuZn21Si3P is a dezincification resistant brass with α + κ microstructure, where κ is a hard Si-rich phase. Its resistance to selective zinc leaching is ensured by the "phosphorus cycle" adopted as an alternative to the analogous "arsenic cycle". The paper investigated the corrosion behaviour and stress corrosion cracking (SCC) susceptibility of two leaded alloys (CW617N and CW602N) and one lead-free silicon brass (CW724R) and investigated this in simulated drinking water (SDW) solutions containing different chloride concentrations. All brass types and particularly CW617N exhibited susceptibility to SCC. No relevant quantitative data provided. It is suggested that leachability data for silicon from lead replacements in plumbing products be generated for Australian conditions to provide information on the form/species of silicon in lead replacements and leachates as well as potential exposure concentrations.

4.3 Risk-based research question analysis

Table 11 Synthesis of extracted data for risk-associated research questions

#	Research Questions	Publication	Response to Research Questions
12	What are the risks to human health from exposure to silicon in Australian drinking water?		No risks to human health from exposure to silicon in drinking water identified in any of the publications reviewed. Most publications did not identify any adverse effects from exposure to silicon in humans, rats, mice, and rabbits. In humans, according to EFSA (2010) and FAO/WHO (1974), apart from occasional case reports of renal stones (for which no dose response information was found in the literature consulted), mainly associated with long-term use of silicate-containing antacids (e.g. as magnesium trisilicate), there is little evidence of adverse effects of orally ingested silicon. Therefore, the human health risks from exposure to silicon in Australian drinking water are likely low, but this is based on limited information.
13	Is there evidence of any emerging risks that require review or further research?		None identified, however the toxicological database for silicon is limited. Clarification of the dose response for development of renal calculi in humans would be useful to confirm the likely low risk of harm to humans from silicon in drinking water.

4.4 Supporting factsheet information research question analysis

Supporting information in fact sheets for chemicals in the Guidelines typically consists of the following (NHMRC and NRMMC 2011):

- **General Description**
- **Typical values in Australian drinking water**
- **Treatment of drinking water**
- **Measurement**

The table below presents the information identified in the literature search conducted which could be used to inform supporting information for a silicon fact sheet. Available information on typical values in Australian drinking water supplies was addressed in **Table 10** as part of an analysis for exposure-related research questions.

Table 12 Synthesis of extracted data for research questions relevant to supporting factsheet information

#	Research Questions	Publication	Response to Research Questions
14	What is silicon used for and how might people be exposed?	**EFSA 2009, 2010**	Silicon occurs naturally in foods as silicon dioxide (SiO_2, silica) and silicates. High levels of silicon are found in foods derived from plants, and particularly cereals, whereas silicon levels are lower in foods from animal sources.
		EFSA 2018a, 2018c	Silicon is an ubiquitous element present in the environment. It is mainly found as insoluble silicates, but small amounts of soluble silicon are naturally present in water, chiefly as orthosilicic acid, $Si(OH)_4$ which is the most bioavailable source of silicon. Silicon dioxide, calcium, magnesium and potassium silicates (E 551–553) are authorised food additives in the European Union (EU).
		EVM 2003	Silica (SiO_2) occurs in nature in several different forms: crystalline (quartz, cristobalite and tridymite) and amorphous. When exposed to water, silicates liberate orthosilicic acid to a concentration of 1-15 mg/L. High levels of silicon are found in foods derived from plants, particularly grains such as oats (4,250 mg/kg wet weight), barley (2,420 mg/kg wet weight) or rice. Levels are lower in foods from animal sources. Beer is also a rich source of silica containing 33-60 mg/kg. Silicon is also found in drinking water as orthosilicic acid. Amorphous silica is used as a food additive, in particular as an anti-caking agent, but also to clarify beverages, control viscosity and as an anti-foaming agent and dough modifier. It is also used as an anti-caking agent and as an excipient in pharmaceuticals for various drug and vitamin preparations. UK food supplements contain up to 500 mg silicon.
		WHO/FAO 1974	Silica, silicic acid and the calcium, magnesium and aluminium salts occur ubiquitously in the environment and some have been used for many years medically. Food contains various amount of SiO_2, for example: potatoes 10.1, milk 2.1, drinking water 7.1, mineral water 22.5, beer 131 gammaSiO_2 per g or cm^3.

#	Research Questions	Publication	Response to Research Questions
		Choucri et al. 2021	Silicon brasses with various compositions were developed to induce grain refining and strength increase or to produce non-toxic Pb- and As-free alloys with good machinability and dezincification resistance. CuZn21Si3P is a dezincification resistant brass with α + κ microstructure, where κ is a hard Si-rich phase. Its resistance to selective Zn leaching is ensured by the "phosphorus cycle" adopted as an alternative to the analogous "arsenic cycle". Actually, in this alloy a significant dealloying process cannot be avoided during long immersions (150 days) in simulated drinking water (SDW).
		Prescha et al. 2012	Used in instant food products.
15	How is the concentration of silicon measured in drinking water?	**Australian Commercial Laboratory Correspondence**	Inductively coupled plasma-mass-spectrometry (ICP-MS), Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES) or Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-AES) according to USEPA Methods SW-846, 3005A, 3010A, 3015A, 3051A, 6010, 6020, 6020A and 29.
		Desai et al. 2012	Spectrophotometric analysis using 'Hach-odyssey spectrophotometer'
		Fujita et al. 2014	ICP-AES and ICP-MS (for suspended material)
		Ghaffari et al. 2021	ICP-MS
		Powell et al. 2005	ICP-OES
		Selianova et al. 2010	Spectrophotometric procedure using crystal violet (MSC) on polyurethane foams (PUF).
		Vertrimurugan et al. 2017	ICP-MS
16	What are the indicators of the risks? How can we measure exposure?	No studies were found specifically evaluating exposure by humans to silicon in drinking water. However, exposure concentrations in drinking water could be monitored using existing commercial analytical techniques (e.g. ICP-MS).	
17	What analytical methods are currently used to measure silicon in drinking water?	**Australian Commercial Laboratory Correspondence, Fujita et al. 2014 Ghaffari et al. 2021 Powell et al. 2005**	ICP-AES, ICP-MS or ICP-OES

#	Research Questions	Publication	Response to Research Questions
18	What are the limits of quantification or limit of reporting for silicon in drinking water?	**Australian Commercial Laboratory Correspondence**	0.05 to 0.5 mg/L
		Ghaffari et al. 2021	10 µg/L
		Selianova et al. 2010	3-6 µg/L
19	How is drinking water treated to minimise silicon concentrations?	**Dayanand et al. 2019**	*"Silica is removed most often by using strongly basic anion exchange resins in the deionization process by distillation or reverse osmosis."*
		Dobbie and Smith 1986	Reverse osmosis reduced tap water Si concentrations from 2.2 mg/L to 0.95 mg/L.
20	What are the current practices to minimise or manage the risks identified?	No data were found to answer this Research Question.	

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APPENDIX A

Literature search screening outcome spreadsheets

Appendix A contents here

APPENDIX B

Data extraction tables – Health-based guidance/guidelines

Existing Health-Based Guidance for Silicon

EFSA 2004

Agency Report Reference: EFSA (2004). Opinion of the Scientific Panel on Dietetic products, nutrition and allergies [NDA] related to the Tolerable Upper Intake Level of Silicon. EFSA Journal 2(5): 60.		
General Information	Date of data extraction	24/05/2023
	Authors	European Food Safety Authority
	Publication date	28/04/2004
	Publication type	Agency Report
	Description	No guidance value was derived in this document. Agency indicates the data are inadequate to derive a tolerable upper intake level.
	Findings	• Silicon has not been shown to be essential for humans. • Silicon occurs naturally in foods as silicon dioxide (silica) and silicates and may also be added as an anti-caking and anti-foaming agent in the form of silica, silicates and dimethylpolysiloxane. Silicate-containing antacids have been widely used for a number of decades. • Silicon in water is present as orthosilicic acid $Si(OH)_4$. Silicic acid exists as monosilicic acid. • Short-term oral exposure with daily intakes of 1,800 mg/kg body weight of sodium or magnesium silicate produces adverse renal effects in dogs, but not in rats (Newberne and Wilson, 1970). Similar doses of silicon dioxide and aluminium silicate did not produce adverse renal effects in either species. Renal effects have been reported in guinea pigs exposed orally to high doses of magnesium trisilicate (50-100 mg/kg body weight/day) (Dobbie and Smith, 1982). • Long-term toxicity studies in rats and mice (Takizawa et al. 1988) show apparent effects on growth at 2,500 and 7,500 mg silica/kg body weight/day, corresponding to 1,170 and 3,500 mg silicon/kg body weight/day, respectively. This effect was not regarded as a toxic effect, but was rather due to nutritional imbalance because of the high dose of silica added to the diet. These studies do not provide any information on the bioavailability of water-soluble forms of silicon from silica, which presumably is low, and hence the systemic load of silicon is not known. The extrapolation of these data to other forms of silicon (such as silicates) is inappropriate. • In humans, apart from occasional reports of renal stones, mainly associated with long-term use of silicate-containing antacids (e.g. as magnesium trisilicate), there is little evidence of adverse effects of orally ingested silicon. The available data are inadequate to derive a tolerable upper intake level. • The estimated typical dietary intake (20-50 mg silicon/day) corresponds to 0.3-0.8 mg/kg body weight/day in a 60 kg person. These intakes are unlikely to cause adverse effects. • Silica is considered not to be genotoxic *in vitro* or *in vivo*.

EFSA 2009

Agency Report Reference: EFSA (2009). Calcium silicate and silicon dioxide/silicic acid gel added for nutritional purposes to food supplements. EFSA Journal 7(6): 1132.		
General Information	Date of data extraction	24/05/2023
	Authors	European Food Safety Authority
	Publication date	05/06/2009
	Publication type	Agency Report
	Description	No guidance value was derived in this document.
	Findings	• Opinion is on safety of calcium silicate, silicon dioxide, silicic acid gel as sources of silicon in food. • Orthosilicic acid [$Si(OH)_4$] is the major silicon species present in drinking water and other liquids, including beer, and is the most readily available source of silicon to man. After oral consumption, the main chemical species by which silicon is absorbed is orthosilicic acid. • No data have been submitted on the bioavailability of silicon from either silicon dioxide or silicic acid gel. However, several studies have shown that silicon present under similar form was readily available from foods and in many cases showed absorption similar to that of silicon from liquids. Furthermore, given the conversion of silicon dioxide/silicic acid to orthosilicic acid upon hydration, and the bioavailability of silicon from orthosilicic acid, the Panel considers that silicon from silicon dioxide/ silicic acid gel is bioavailable. • The UK Expert group on Vitamins and Minerals (EVM) set a Safe Upper Level for daily consumption of silicon at 700 mg silicon/day for adults over a lifetime (equivalent to 12 mg silicon/kg body weight/day for a 60 kg adult). • The Panel concluded that, in view of the Safe Upper Level for silicon of 700 mg silicon/day established by the EVM for supplemental use and of 2,500 mg calcium/day for adults established by the Scientific Committee for Food (SCF), the exposure to calcium and to silicon resulting from the proposed uses of calcium silicate as a source of respectively silicon and calcium in food supplements, the use of calcium silicate in food supplements at the proposed use levels is of no safety concern, provided that it complies with the specifications for its use as a food additive. • The Panel also concludes that the use of silicon dioxide up to 1500 mg SiO_2/day (equal to 700 mg/day) and of silicic acid gel to supply up to 200 mg silicon/day, added to food supplements, is of no safety concern.

EFSA 2010

Agency Report Reference: EFSA (2010). Selected trace and ultratrace elements: Biological role, content in feed and requirements in animal nutrition – Elements for risk assessment. EFSA Supporting Publications, European Food Safety Authority. 7**:** 68E.		
General Information	Date of data extraction	24/05/2023
	Authors	Van Paemel M, Dierick N, Janssens G, Fievez V, De Smet S
	Publication date	23/07/2010
	Publication type	Agency Report written by Ghent University for EFSA
	Description	No guidance value was derived in this document.
	Findings	• Extremely high intakes of silicon are required to induce only minor effects on growth and reproduction. The harmful effects of an excessive silicon intake in animals include a depression in roughage dry matter digestibility and formation of urinary calculi for ruminants, and depressed growth and abnormal reproduction for rats. • The absorbability of silicon is considerably influenced by the amount ingested. • Silicon is not considered to be genotoxic *in vitro* or *in vivo*. • There are no reports on human toxicity following intake of silicon occurring naturally in food. Humans have for decades consumed amorphous silicates as food additives used for anti-foaming and anti-caking purposes without any reported deleterious effects. • Silicon in the form of magnesium trisilicate has been used as an antacid for several decades. The only related adverse effect is the formation of renal silicate stones. • EVM established an upper intake level (UL) for supplemental silicon of 700 mg/day for adults. EFSA and Institute of Medicine (IOM) considered the available data insufficient to establish an UL value. • If inhaled at high concentrations over prolonged periods, certain forms of silica can cause silicosis. Inhaled silica particles can cause tissue damage that ultimately results in fibrosis which reduces the efficiency of the lungs and results in shortness of breath. The carcinogenicity of inhaled silica particles is due to local tissue damage and inflammation with the production of reactive oxygen species, which overwhelm cellular defences and damage DNA. This process is considered not to be relevant to oral exposure to silica or silicon.

EFSA 2018a

Agency Report Reference: EFSA (2018a). Safety of orthosilicic acid-vanillin complex (OSA-VC) as a novel food ingredient to be used in food supplements as a source of silicon and bioavailability of silicon from the source. EFSA Journal 16(1): e05086.		
General Information	Date of data extraction	24/05/2023
	Authors	EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS)
	Publication date	21/11/2017

Agency Report Reference: EFSA (2018a). Safety of orthosilicic acid-vanillin complex (OSA-VC) as a novel food ingredient to be used in food supplements as a source of silicon and bioavailability of silicon from the source. EFSA Journal 16(1): e05086.		
	Publication type	Agency Report
	Description	No guidance value was derived in this document.
	Findings	• Scientific opinion deals with safety of orthosilicic acid-vanillin complex (OSA-VC) as a novel food ingredient for use as a source of silicon in food supplements. This was considered potentially relevant to this work, since OSA-VC dissociates into orthosilicic acid and vanillin. Orthosilicic acid is the form of silicon typically present in water. • The daily consumption of OSA-VC at the daily dose recommended by the applicant would provide a supplemental intake of silicon of approximately 10–18 mg/day which would result in an estimated total intake from supplement use and from the diet of roughly 30–70 mg silicon/day, thus not exceeding the safe upper level of supplemental silicon intake of 700 mg/day of Si for adults as set by the UK Expert group on Vitamins and Minerals (EVM) in 2003. • The Panel concluded that there would be no safety concern with the proposed use and use level of OSA-VC as a novel food ingredient intended to be used as a source of silicon in food supplements for the adult population as proposed by the applicant.

EFSA 2018c

Agency Report Reference: EFSA (2018c). Re-evaluation of calcium silicate (E 552), magnesium silicate (E 553a(i)), magnesium trisilicate (E 553a(ii)) and talc (E 553b) as food additives. EFSA Journal 16(8): e05375.		
General Information	Date of data extraction	24/05/2023
	Authors	European Food Safety Authority Panel on Food Additives and Nutrient Sources added to Food (ANS)
	Publication date	27/06/2018
	Publication type	Agency Report
	Description	No guidance value was derived in this document.

	Findings	• Re-evaluation of safety of calcium silicate (E552), magnesium silicate (E553a) and talc (E553b) when used as food additives. • The Panel considered that silicate anion from both calcium silicate or magnesium trisilicate was absorbed to a limited extent in rats. No data were available for magnesium silicate. • Based on a 2-year study with calcium silicate in rats, the Panel considered that at high doses (up to 5,000 mg/kg body weight (bw) per day), there was evidence of silicon accumulation in the liver and kidney. The Panel considered that limited data in humans indicated that the silicate anion from magnesium trisilicate is absorbed to a limited extent, then excreted in the urine (as determined from urinary silicon measurements). No human data were available for calcium silicate or magnesium silicate; however, the Panel considered that a read-across approach was appropriate and considered that silicate anion from both calcium silicate or magnesium silicate would behave similarly. • Calcium silicate, magnesium silicate and talc have a low acute oral toxicity. No studies were available for magnesium trisilicate. • No adverse effects were observed in short-term toxicity studies in rats with calcium silicate, magnesium trisilicate or talc. The kidney effects observed in dogs were most probably related to the large amount of test compound consumed as a bolus dose by the animals. The effects on the kidney reported in guinea pigs could be due to higher concentrations of silicate in the primary urine as a consequence of lower glomerular filtration rates in guinea pigs (2.29 mL plasma/min per kg) as compared to rats (4.63 mL plasma/min per kg). The Panel noted that in humans the glomerular filtration rate (3.56 mL plasma/min per kg) is higher than in guinea pigs and, furthermore, kidney effects have not been found in humans in the EudraVigilance database despite the wide and long-term use of high doses of magnesium trisilicate (up to 4 g/person per day) as an antacid over decades. • In a 2-year study in rats, not performed according to current standards, calcium silicate had no effect on mortality at a dose up to 5,000 mg/kg bw per day. No gross pathology or histopathological findings that could be attributed to calcium silicate were observed in the 500 and 2,500 mg/kg bw per day groups. However, in the absence of clinical chemistry data, given the respiratory infection of animals and only 15 animals/sex per group, the Panel considered that this study was too limited to conclude on the chronic toxicity of calcium silicate. However, the Panel noted that no carcinogenic effects were reported in this study. There were no data for oral chronic toxicity/carcinogenicity of talc. • Prenatal developmental toxicity studies with calcium silicate by gavage during organogenesis in mice, rats and hamsters, and with talc in mice and rats, up to 1,600 mg/kg bw per day (the highest dose tested), showed no dose-related developmental effects. • The Panel states treatment with silicate antacid drugs such as magnesium trisilicate resulting in urinary calculi are seldom found in humans (0.1-0.2% of all urinary stones), but describe a few case reports: i) one case with renal colic from taking 2 g

Agency Report Reference: EFSA (2018c). Re-evaluation of calcium silicate (E 552), magnesium silicate (E 553a(i)), magnesium trisilicate (E 553a(ii)) and talc (E 553b) as food additives. EFSA Journal 16(8): e05375.		
		magnesium trisilicate (as an antacid) with every meal for many years, ii) cases are mostly found in adults but have been described in rare cases in children where they were associated with consumption of milk thickener containing 5.5% silicates in one case of a 6-month old boy, or iii) milk powder dissolved in silicate-rich mineral water (estimated daily intake 200 mg silicate) in a 10-month old boy. • The Panel noted that cases of renal calculi were rarely reported in the EudraVigilance database considering the high number of exposed humans to magnesium trisilicate as an antacid. The Panel applied the WHO algorithm for assessing the association between adverse events and drug intake and found that the association between silicate antacid use and renal calculi was 'possible' but not 'definite', which does not exclude that the occurrence of renal calculi and intake of silicates would be a chance finding. • Due to the limitations in the available toxicological database for individual silicates, the Panel was unable to derive ADIs for calcium silicate (E 552), magnesium silicate (E 553a(i)), magnesium trisilicate (E 553a(ii)) and talc (E 553b). • Based on the food supplement scenario considered as most representative for risk characterisation, exposure to silicates (E 552–553) for all population groups was below the maximum daily dose of magnesium trisilicate used as an antacid (4 g/person per day).

EVM 2003

Agency Report Reference: EVM (2003). Safe upper limits for vitamins & minerals, Expert Group on Vitamins and Minerals.		
General Information	Date of data extraction	24/05/2023
	Authors	Expert Group on Vitamins and Minerals
	Publication date	May 2003
	Literature search timeframe	Up to September 2001
	Publication type	Agency review
	Peer reviewed?	Yes
	Country of origin	UK
	Source of funding	UK Government
	Possible conflicts of interest	No (all possible conflicts of interest declared)
Health considerations	Guideline value type (e.g. oral TRV, drinking water guideline)	Oral TRV (termed 'Safe Upper Level' or SUL)
	Exposure timeframe	Lifetime (SUL represents an intake that can be consumed daily over a lifetime without significant risk to health on the basis of available evidence).

Agency Report Reference: EVM (2003). Safe upper limits for vitamins & minerals, Expert Group on Vitamins and Minerals.		
	Critical human health endpoint	Few data are available on the oral toxicity of silicon in humans and they are inadequate for risk assessment. Therefore, the animal data have been considered for this purpose. No adverse effects noted in chronic studies in mice and rats fed amorphous silica in the diet.
	Justification provided by agency for critical endpoint	See above. Adverse effects noted at 50,000 ppm (transient reductions in growth rates in mice and reduced liver weights in female rats) were likely due to nutritional imbalance and are not considered relevant to human exposure.
	Critical study(ies) underpinning point of departure	Takizawa et al. 1988 • Groups of 40 B6C3F1 mice and 40 Fisher rats were fed 0, 12500, 25000 or 50000 ppm (5%) SYLOID (silicon dioxide) in the diet for up to 21 months (in mice this was equivalent to 1,900 – 7,500 mg/kg bw silica or 900 to 3500 mg silicon). • In mice, top dose (equivalent to 7,500 mg/kg bw/day silicon dioxide, or 3,495 mg silicon/kg bw/day) was considered to be a NOAEL. • In rats, top dose (equivalent to 2,500 mg/kg bw/d silicon dioxide or 1,165 mg silicon/kg bw/day) was regarded as NOAEL.
	Species for critical study(ies)	Rats and mice
	Point of departure type (e.g. NOAEL, LOAEL, $BMDL_{10}$, etc)	NOAEL
	Point of departure value (include units)	50,000 ppm silica in diet (2,500 mg/kg bw/d in rats, 7,500 mg/kg bw/d in mice). The study in rats was used to establish SUL.
	Uncertainty factor(s) & rationale	100 (10x for inter-species variation, 10x for human variability)
	Guideline value (include units)	25 mg/kg bw/d supplemental silica (equivalent to 12 mg/kg bw/d elemental silicon or 700 mg/day for a 60kg adult).
	Mode of action for critical health endpoint	No data identified.
	Genotoxic carcinogen?	Inorganic silicon compounds do not appear to have significant genotoxic potential.
	Identified sensitive sub-populations	None identified.
	Any non-health based considerations?	No.
Exposure considerations	Principal routes of exposure in general population	• Primarily the diet: ○ High levels of silicon found in foods derived from plants (e.g. grains and oats, barley and rice). ○ Beer is also a rich source of silica. ○ Silicon is found in drinking water as orthosilicic acid.
	Levels in drinking water supplies (include location)	Inferred to be 5 mg/L from statement that "*consumption of 2 L/day drinking water could result in consumption of up to 10 mg silicon.*"

Agency Report Reference: EVM (2003). Safe upper limits for vitamins & minerals, Expert Group on Vitamins and Minerals.		
	Any special considerations to exposure levels (e.g. higher in drought?)	Exposure to high levels of airborne silica occurs in certain occupations (e.g. miners, quarry workers, sand blasters).
	Typical exposure in general population (include units for intakes & location)	• Food: Up to 50 mg/day • Supplements: Up to 500 mg/L • Water: 10 mg/day (assuming 2 L/day consumption and maximum reported level of 5 mg/L in UK) • Total maximum intake: 560 mg/day • No potential high intake groups were identified
Risk Summary	Any risks to human health from drinking water identified in agency document?	No
	Any emerging risks identified?	No
	Any other relevant information that should be captured?	Bioavailability of silicon depends on the solubility of the compound or the speciation. Silicic acid is the form absorbed from the gastrointestinal tract at approximately 20-75%. A study in rats and turkeys suggested that short term intakes of 500 and 270 ppm dietary silicon respectively as silicates may result in reduced growth and other changes in mineral levels. This study used an organic silicon compound (tetraethylorthosilicate), sodium zeolite, which contains aluminium, and sodium silicate, which is the compound most representative of silicon in food. A more detailed chronic study was chosen as the basis for the SUL in which it was indicated that chronic intakes of diets containing 12,500 and 25,000 ppm amorphous silica were not associated with any adverse effect in rats and mice respectively.

FAO/WHO 1969

Agency Report Reference: FAO and WHO (1969). Toxicological evaluation of some food colours, emulsifiers, stabilizers, anti-caking agents and certain other substances, Food Agriculture Organization of the United Nations and World Health Organization.		
General Information	Date of data extraction	24/05/2023
	Authors	Joint FAO/WHO Expert Committee on Food Additives, World Health Organization
	Publication date	1969
	Publication type	Agency Report
	Description	A 'Not limited' acceptable daily intake was specified except for Good Manufacturing Practice. It is noted that this ADI has since been withdrawn.
	Findings	• Information in this report was updated in next publication (FAO/WHO 1974) and has not been repeated here.

FAO/WHO 1974

Agency Report Reference: FAO and WHO (1974). Silicon Dioxide and Certain Silicates, Food Agriculture Organization of the United Nations and World Health Organization.		
General Information	Date of data extraction	24/05/2023
	Authors	Joint FAO/WHO Expert Committee on Food Additives, World Health Organization
	Publication date	1974
	Publication type	Agency Report
	Description	A 'Not limited' acceptable daily intake was specified for silicon dioxide and certain silicates except magnesium silicate and talc. For magnesium silicate and talc this was 'Temporarily not limited'. It is noted that these ADIs have since been withdrawn.
	Findings	• Silica, silicic acid and calcium, magnesium and aluminium salts occur ubiquitously in the environment and some have been used for many years medically. • There appears to be little retention in any organ of the body even if animals ingest large amounts of silicates in their food. • A 2-generation reproduction study with oral administration of 100 mg/kg bw/day amorphous silica to rats found no malformations or any other adverse effects. In a 2-year study at the same dose, no adverse effects were observed. • Groups of 15 male and 15 female rats were fed diets containing silica at concentrations of 0, 1, 3, and 5% for 90 days; no evidence of treatment-related toxicity observed (Elsea 1958b, as cited in FAO and WHO 1974). Same thing (no adverse effects) after feeding 500 mg/kg/d to rats for 6 months (Leuschner 1963, as cited in FAO and WHO 1974). • Dogs fed either silicon dioxide, aluminium silicate, sodium silicate or magnesium trisilicate for 4 weeks equivalent to 0.8 g/kg/day of silicon dioxide resulted in polydipsia and polyuria in a few animals fed sodium silicate and magnesium trisilicate. Histopathology revealed characteristic renal lesions in all dogs fed these two compounds but not in other groups. • 60-100 g daily for 3-4 weeks of 12% amorphous silicic acid administered orally to patients suffering from gastritis or enteritis were tolerated without adverse effects. Only 1/1000th of the substance administered was excreted in urine (Sarre 1953, as cited in FAO and WHO 1974). • Available data on orally administered silica and silicates appear to substantiate the biological inertness of these compounds. Any silicate absorbed is excreted by the kidneys without evidence of toxic accumulation in the body, except for the reported damage to dog kidneys by magnesium trisilicate and sodium silicate.

APPENDIX C

Data extraction tables – Full Review for Health-based Studies

Austin 1978

Publication Reference: Austin J. H. (1978). Silicon Levels in Human Tissues. Biochemistry of Silicon and Related Problems. G. Bendz, I. Lindqvist and V. Runnström-Reio. Boston, MA, Springer US: 255-268.		
General Information	Date of data extraction	25/05/2023
	Authors	Austin JH
	Publication date	1978
	Publication type	Book chapter
	Peer reviewed?	No
	Country of origin	USA
	Source of funding	Not stated (authors are from a Medical Center)
	Possible conflicts of interest	No conflict of interest statement is included in the book/chapter.
Study characteristics	Aim/objectives of study	Reports on an animal experiment as part of a larger discussion of Si in human tissues.
	Study type/design	Experimental animal study
	Study duration	4 months
	Type of water source (if applicable)	Reagent grade $Na_2SiO_3.9H_2O$ used (contains 10.11% Si) to make solutions provided as drinking water to the animals. Silica solutions containing more than 0.2% Si were soluble initially, but flocculated subsequently.
Population characteristics	Population/s studied	27 mice, 3 rabbits, 1 rhesus monkey, 1 basset hound (Selection criteria not specified)
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	See above
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Si in drinking water from mixing reagent grade $Na_2SiO_3.9H_2O$ with water.
	Exposure concentrations (if applicable)	0.005 or 0.1% Si in drinking water for 4 months
	Comparison group(s)	None (not applicable)
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• No gross or microscopic changes were apparent in brains, hearts, kidneys, livers or spleens, nor were consistent behavioural changes apparent in animals. • Mice exposed to 0.1% Si in drinking water for 2-17 months showed no consistent elevation in Si levels in their organs compared with controls.
	How outcome was assessed	

Publication Reference: Austin J. H. (1978). Silicon Levels in Human Tissues. Biochemistry of Silicon and Related Problems. G. Bendz, I. Lindqvist and V. Runnström-Reio. Boston, MA, Springer US**:** 255-268.		
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	See above
Statistics (if any)	Statistical method used	Not applicable (no statistical analysis undertaken)
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	Soluble Si was not toxic at the doses used. The amount that could be administered in drinking water was, however, limited by formation of precipitate.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• Very limited experimental information provided in study. Small sample sizes. • Results suggest 0.005% or 0.1% solubilised Si in drinking water does not result in adverse effects in mice, rabbits, monkey or dog. These percentages equate to 50 and 1,000 mg Si/L. • Study reporting quality is low; very limited detail provided. Nevertheless, risk of bias analysis was undertaken.
	Notes on study quality, e.g. gaps, methods	

Burton et al. 1980

Publication Reference: Burton A. C., Cornhill J. F. and Canham P. B. (1980). Protection from cancer by 'silica' in the water-supply of U.S. cities. J Environ Pathol Toxicol 4(1): 31-40.		
General Information	Date of data extraction	25/05/2023
	Authors	Burton AC, Cornhill JF, Canham PB
	Publication date	1980
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Canada
	Source of funding	Not stated (authors are from a University)
	Possible conflicts of interest	No conflict of interest statement is included in the paper.
Study characteristics	Aim/objectives of study	To explore in more detail a negative association found for SiO_2 in drinking water of 100 largest US cities and age-adjusted death rates from cancer.
	Study type/design	Observational study (cross-sectional)
	Study duration	Not applicable

Publication Reference: Burton A. C., Cornhill J. F. and Canham P. B. (1980). Protection from cancer by 'silica' in the water-supply of U.S. cities. J Environ Pathol Toxicol 4(1): 31-40.		
	Type of water source (if applicable)	Raw and finished drinking water.
Population characteristics	Population/s studied	US population of 100 cities
	Selection criteria for population (if applicable)	
	Subgroups reported	Males and females
	Size of study	Unclear (100 cities)
Exposure and setting	Exposure pathway	Drinking water
	Source of chemical/contamination	For most cities, the average concentration in raw water supply was comparable to that of finished water and therefore hardly altered by treatment. Therefore, the source is natural mineralogy.
	Exposure concentrations (if applicable)	90% of cities have concentrations in finished water <15 mg/L.
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Colour-reaction with ammonium molybdate in an acid medium. This will react to the great variety of silicates and silicic acids, as well as to SiO_2.
	Water sampling methods (monitoring, surrogates)	Used data from US Geological Survey. Incubation for one hour with sodium bicarbonate in recommended as a means of making all 'silica' available for reaction with the molybdate. However, study authors have no information as to how much of the SiO_2 concentration represents SiO_2 as such and how much is soluble silicates.
Results (for each outcome)	Definition of outcome	See statistical method used section below.
	How outcome was assessed	
	Method of measurement	Not stated
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not stated
Statistics (if any)	Statistical method used	• Compared mean death rate for the cities with <15ppm and standard error of this mean with mean and SD for cities with >15ppm by T-test. • Then computed regression slope of death rates vs. SiO_2 for concentrations <15ppm and statistical significance of slope. • Adjusted for other factors found previously to also be negatively correlated.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	R = -0.417, p<0.1 for male, R = -0.313, P=0.01 for female (0-15 mg/L)
Author's conclusions	Interpretation of results	The results suggest a protective effect of cancer from SiO_2 (up to a certain saturation level) in drinking water
	Assessment of uncertainty (if any)	Mechanism by which SiO_2 does this is unknown but speculated by authors.

Publication Reference: Burton A. C., Cornhill J. F. and Canham P. B. (1980). Protection from cancer by 'silica' in the water-supply of U.S. cities. J Environ Pathol Toxicol 4(1): 31-40.		
Reviewer comments	Results included/excluded in review (if applicable)	• For concentrations 0 to 15 mg/L, there is a significant regression and negative correlation. For the rest of the range of concentrations (15-70 mg/L) there is no further significant reduction in death rates. • This is an observational study and the findings may be due to chance. It is unclear from the publication if other potential confounders have been controlled for. • RoB assessment was undertaken.
	Notes on study quality, e.g. gaps, methods	

Cetin et al. 2017

Publication Reference: Cetin I., Nalbantcilar M. T., Tosun K. and Nazik A. (2017). How Trace Element Levels of Public Drinking Water Affect Body Composition in Turkey. Biol Trace Elem Res 175(2): 263-270.		
General Information	Date of data extraction	25/05/2023
	Authors	Cetin I, Nalbantcilar MT, Tosun K, Nazik A
	Publication date	2017
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Turkey
	Source of funding	Not stated (authors are from a University)
	Possible conflicts of interest	The authors report no conflicts of interest.
Study characteristics	Aim/objectives of study	To assess the relationship between trace elements in public drinking water and body composition in average, overweight and obese individuals in Turkey.
	Study type/design	Observational study (cross-sectional)
	Study duration	Not applicable
	Type of water source (if applicable)	Wells supplying water to residential areas for drinking.
Population characteristics	Population/s studied	423 participants (all female, aged 18-50 years) who applied at the Diet Polyclinic of Batman Regional State Hospital from Oct 2015 until late March 2016. Grouped as overweight (n=143), obese (n=138) or control (n=142). All lived in Batman Province, and no participants were taking any regular medication at the time of study, nor were any diagnosed with any systemic disease, diabetes and cancer or any major diseases aside from obesity. Some participants were excluded because they had recently consumed bottled drinking water or drank water from different water resources.
	Selection criteria for population (if applicable)	
	Subgroups reported	Overweight (n=143), obese (n=138) or control (n=142)
	Size of study	423 participants
Exposure and setting	Exposure pathway	Drinking water from wells supplying water to all residential areas of Batman, Turkey.

Publication Reference: Cetin I., Nalbantcilar M. T., Tosun K. and Nazik A. (2017). How Trace Element Levels of Public Drinking Water Affect Body Composition in Turkey. Biol Trace Elem Res 175(2): 263-270.		
	Source of chemical/contamination	Not stated.
	Exposure concentrations (if applicable)	Si levels in drinking water for the 16 samples ranged from 5.3 to 16 mg/L.
	Comparison group(s)	Healthy individuals (non-obese, not overweight).
Study methods	Water quality measurement used	Laboratory analyses were conducted on 16 samples in accordance with the standard methods of American Public Health Association.
	Water sampling methods (monitoring, surrogates)	Water samples from wells supplying water to Batman were obtained from July to December 2015. Samples numbered 1–16 were taken from wells in Selmo Formation, whereas all others were collected from wells in the old alluvium area. Without taking care of the sources, each sample was collected after water was pumped from the respective well for nearly 1 h and later filled into sterilised containers along with 10 % hydrochloric acid to yield pH levels <2.
Results (for each outcome)	Definition of outcome	• Correlation of body mass index values with concentrations of elements. • Body weight values showed significant positive correlations with Ni content in all the participants ($p < 0.05$) as BMI values with Al ($p < 0.05$). Also in all the participants, Ni, Si and B content demonstrated significant positive correlations with percentage of obesity ($p < 0.05$), and Ni in particular showed significant positive correlation with basal metabolic rate (BMR) values, activity calories and total activity ($p < 0.05$). However, authors did not detect any significant correlation between Li, Pb, Sn, Ba and Rb content in drinking water and any component of bioelectrical impedance analysis (BIA) results.
	How outcome was assessed	
	Method of measurement	Standard BMI measurement.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	See above
Statistics (if any)	Statistical method used	• Statistical analyses were conducted by using the Statistical Package for the Social Sciences version 15.0 (SPSS Inc., Chicago, IL, USA) and Sigma Stat 3.5. Normality of data distribution was evaluated with the Kolmogorov–Smirnov test, and a one-way analysis of variance was used to investigate the mean differences between the groups to suit normal distribution; however, results of the Kruskal–Wallis test did not fall within the normal distribution. • Differences in the distribution of categorical variables were then evaluated with the chi-square test, and Pearson's and Spearmen's correlation coefficients were used to pinpoint the relationship between body composition and element levels in water samples. Categorical variables were stated as numbers, and perpetual variables were expressed as M ± SD or median (25th–75th percentile) as appropriate. Statistical significance was set at 0.05.
	Details on statistical analysis	

Publication Reference: Cetin I., Nalbantcilar M. T., Tosun K. and Nazik A. (2017). How Trace Element Levels of Public Drinking Water Affect Body Composition in Turkey. Biol Trace Elem Res 175(2): 263-270.		
	Relative risk/odds ratio, confidence interval?	-
Author's conclusions	Interpretation of results	• The observed association of Si with BMI and % obesity found in the present study is intriguing, as Si has not yet been established as being essential for human body. • Further studies should therefore seek to determine levels of Si in water giving the element's effects on the body, especially in terms of body composition.
	Assessment of uncertainty (if any)	Not applicable
Reviewer comments	Results included/excluded in review (if applicable)	• The study suggests a positive correlation of Si concentration in drinking water and % obesity, but data is too limited to draw any conclusions from this. The authors also conclude that further studies are needed. • As this study is not considered a potential key study for guideline/guidance value development, it was excluded from further assessment and RoB analysis was not undertaken.
	Notes on study quality, e.g. gaps, methods	

Dayanand et al. 2019

Publication Reference: Dayanand A, Vasantha and Viplav (2019). Correlating silica content in drinking water with kidney failure in Telangana-a basic study. Journal of applicable chemistry 8(4): 1592-1598.		
General Information	Date of data extraction	25/05/2023
	Authors	Dayanand A, Vasantha A, Shukla VD
	Publication date	2019
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	India
	Source of funding	Not stated (authors are from a City College)
	Possible conflicts of interest	No conflict of interest statement was included in the paper.
Study characteristics	Aim/objectives of study	Select drinking water from the epidemic areas of kidney failure in India and correlate with the silica content in it.
	Study type/design	Observational study (cross-sectional)
	Study duration	Not applicable
	Type of water source (if applicable)	Presumed to be drinking water But unclear.
Population characteristics	Population/s studied	Selected mining areas of Kothagudem.
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable

Publication Reference: Dayanand A, Vasantha and Viplav (2019). Correlating silica content in drinking water with kidney failure in Telangana-a basic study. Journal of applicable chemistry 8(4): 1592-1598.		
	Size of study	Not applicable (study only measures Si in drinking water, but makes no actual correlation with kidney disease in populations).
Exposure and setting	Exposure pathway	Drinking water
	Source of chemical/contamination	Not stated.
	Exposure concentrations (if applicable)	Reverse osmosis (RO) water (control): 2.8 mg/L Bore water in mining area: 62-68 mg/L
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Ammonium molybdate method. The intensity of the yellow colour is proportional to the concentration of 'molybdate reactive' silica. To detect the presence of molybdate-unreactive silica, digestion sample with $NaHCO_3$ before colour development. This digestion is not necessarily sufficient to convert all molybdate-unreactive silica polymers may require extended (time) under pressure for complete conversion. The authors state to omit digestion if all the silica is known to react with molybdate.
	Water sampling methods (monitoring, surrogates)	Approximately 1 mg SiO_2/L can be detected in 50 mL of water. All reagents must be stored in plastic containers.
Results (for each outcome)	Definition of outcome	• No health outcomes were actually investigated in the study although the title and abstract insinuate it was. • Study only measures Si in drinking water, but makes no actual correlation with kidney disease in populations drinking the water.
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	See above
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	-
Author's conclusions	Interpretation of results	The study authors conclude *"The results show that drinking water from reverse osmosis is devoid of silica. But, in other selected mining areas of this project shows high level of silica content, resulting in kidney failures among these areas."*
	Assessment of uncertainty (if any)	Not applicable
Reviewer comments	Results included/excluded in review (if applicable)	

Publication Reference: Dayanand A, Vasantha and Viplav (2019). Correlating silica content in drinking water with kidney failure in Telangana-a basic study. Journal of applicable chemistry 8(4): 1592-1598.		
	Notes on study quality, e.g. gaps, methods	• The manner in which the authors express the aim/objective of the project appears quite biased: "*This project is objected to prove that silica present in drinking water is also one of the reasons for kidney failure of the people in those areas*." • No health outcomes were actually investigated in the paper although the title and abstract insinuate it was. • Study only measures Si in drinking water, but makes no actual correlation with kidney disease in populations drinking the water. • Poor quality write-up and clearly biased. • As paper was not considered a potentially key study for guidance/guideline value development, it was excluded from further review and risk of bias analysis was not undertaken.
Other information		*"Silica is removed most often by using strongly basic anion exchange resins in the deionization process by distillation or reverse osmosis."*

Dobbie and Smith 1982

Publication Reference: Dobbie J. W. and Smith M. J. (1982). Silicate nephrotoxicity in the experimental animal: the missing factor in analgesic nephropathy. Scott Med J 27(1): 10-16.		
General Information	Date of data extraction	25/05/2023
	Authors	Dobbie JW and Smith MJB
	Publication date	1982
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	UK
	Source of funding	Funding sources not specified (authors are from Glasgow Royal Infirmary)
	Possible conflicts of interest	No conflict of interest statement was included in the paper.
Study characteristics	Aim/objectives of study	To determine the potential nephrotoxicity of silicon containing materials in drinking water to guinea pigs
	Study type/design	Experimental animal study
	Study duration	5 days/week for 4 months
	Type of water source (if applicable)	Drinking water containing three silicon-containing compounds (magnesium trisilicate BP, crushed quartz and crushed Arran granite) at 250 mg/L.
Population characteristics	Population/s studied	Three groups of 6 male guinea pigs (weight 500-700g)
	Selection criteria for population (if applicable)	
	Subgroups reported	6/group (3 exposure groups)
	Size of study	24 guinea pigs

Publication Reference: Dobbie J. W. and Smith M. J. (1982). Silicate nephrotoxicity in the experimental animal: the missing factor in analgesic nephropathy. Scott Med J 27(1): 10-16.		
Exposure and setting	Exposure pathway	Drinking water (suspension shaken during working hours every half hour)
	Source of chemical/ contamination	Magnesium trisilicate, crushed quartz or crushed granite
	Exposure concentrations (if applicable)	Tap water = 10 µmol/L (0.28 mg/L), magnesium trisilicate = 267 µmol/L (7.5 mg/L), granite= 29 µmol/L (0.8 mg/L)
	Comparison group(s)	-
Study methods	Water quality measurement used	Concentrations of soluble Si in tap water and in the supernatant of the suspension was measured by Atomic Absorption Spectrophotometry (AAS)
	Water sampling methods (monitoring, surrogates)	Rocks were crushed and ball-milled to give particles ranging from 0.5-40 µm. A suspension (250 mg/L) was made in Glasgow tap water for each of the three substances.
Results (for each outcome)	Definition of outcome	• At autopsy all animals receiving magnesium trisilicate (6/6) showed a focal tubule-interstitial nephritis mainly affecting the distal nephron. Similar but less intense lesions were encountered in two animals (2/6) receiving crushed quartz. No renal lesions were found in control group or in animals receiving crushed granite. • Following ingestion of magnesium trisilicate, significant increases in urinary excretion of Si were demonstrated in two healthy human adults using AAS.
	How outcome was assessed	
	Method of measurement	Histopathology / AAS
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	18 exposed, 6 control animals. Urinary excretion monitored in 2 healthy humans.
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	-
Author's conclusions	Interpretation of results	• Concentration of Si in tapwater in the UK ranged from 7-256 µmol/L (0.2-7.2 mg/L). • An estimated dose of 50-100 mg magnesium trisilicate/kg/day resulted in renal damage in guinea pigs in 4 months.
	Assessment of uncertainty (if any)	• It is a commonly held belief that ingested silicates are both inert and non-absorbable. There is, however, in the world literature sufficient information, albeit sketchy and somewhat obscure, to correct this misconception. • There are many intriguing and as yet unresolved questions concerning the effect on the human kidney of a variety of Si compounds to which man is currently exposed. Nevertheless, a plea to nephrologists, pharmacologists, drug companies, food manufacturers, committees on drug and food safety, and water boards for a greater awareness of what is already known of the subject is surely not unreasonable.

Publication Reference: Dobbie J. W. and Smith M. J. (1982). Silicate nephrotoxicity in the experimental animal: the missing factor in analgesic nephropathy. Scott Med J 27(1): 10-16.		
Reviewer comments	Results included/excluded in review (if applicable)	• Single dose of different silicon compounds given to guinea pigs. Authors report the dose of magnesium trisilicate administered in drinking water for 4 months resulting in nephrotoxicity as 50-100 mg/kg/d (i.e. 16-32 mg Si/kg/d). • Potentially provides information on dose response of Si. Included in risk of bias analysis.
	Notes on study quality, e.g. gaps, methods	

Dobbie and Smith 1986

Publication Reference: Dobbie J. W. and Smith M. B. (1986). Urinary and serum silicon in normal and uraemic individuals. Ciba Found Symp 121: 194-213.		
General Information	Date of data extraction	25/05/2023
	Authors	Dobbie JW and Smith MJB
	Publication date	1986
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	UK
	Source of funding	National Kidney Research Fund
	Possible conflicts of interest	No conflict of interest statement was included in the paper.
Study characteristics	Aim/objectives of study	To inform and provide information on the renal handling of silicon in humans, in healthy and uremic individuals.
	Study type/design	Human controlled trial
	Study duration	24-hour
	Type of water source (if applicable)	Tap water with or without reverse osmosis.
Population characteristics	Population/s studied	• Various populations (different patients undergoing dialysis). • Urinary excretion of Si in healthy individuals and one patient on different diets (96 - >360 µmol Si/day) • 10-72 x 24-hour urinary collections • Serum Si was studied in four groups of patients undergoing dialysis: Group 1 (low tap water Si: 14 µmol/L or 0.4 mg/L), Group 2 (intermediate tap water Si: 78 µmol/L or 2.2 mg/L), Group 3 (intermediate tap water Si, reverse osmosis used: 34 µmol/L or 0.95 mg/L), Group 4 (high tap water Si: 142 µmol/L or 4 mg/L).
	Selection criteria for population (if applicable)	
	Subgroups reported	Various (see above)
	Size of study	Varies depending on investigation
Exposure and setting	Exposure pathway	Diet or dialysis fluid
	Source of chemical/ contamination	Tap water

Publication Reference: Dobbie J. W. and Smith M. B. (1986). Urinary and serum silicon in normal and uraemic individuals. Ciba Found Symp 121: 194-213.		
	Exposure concentrations (if applicable)	Varied (see above)
	Comparison group(s)	-
Study methods	Water quality measurement used	Not specified
	Water sampling methods (monitoring, surrogates)	Not specified
Results (for each outcome)	Definition of outcome	Various studies undertaken to see what behaviour of Si is in serum and urine after ingestion of Si in diet or exposure to dialysis liquid containing Si.
	How outcome was assessed	
	Method of measurement	Various
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Various
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	-
Author's conclusions	Interpretation of results	• Urinary Si is mainly derived from dietary intake and, on a normal diet, humans excrete a large amount of Si in urine. Serum Si is maintained within a relatively narrow range in healthy individuals, although a 2-3 fold increase can occur briefly during silicate ingestion. • With increasing renal functional impairment, urinary elimination of Si decreases and serum Si rises. The concentration of Si in the serum of uraemic patients (serum creatinine > 450 µmol/l) is consistently two to three times that found in normal healthy individuals. After successful renal transplantation, the raised levels of serum Si fall to near-normal values by three months. • The findings in dialysed patients demonstrate a close correlation between Si concentration in the serum and dialysate for each centre studied, suggesting that the Si content of the water supply is the major factor in the geographical variation in serum Si in dialysed patients. • Suspicion of Si as a potential nephrotoxic agent in humans comes from its suggested role as a causative factor in Balkan nephropathy (Marcovic & Arambasic 1971), from earlier work on the incidence of renal lesions in silicosis (Kolev et al. 1970), and from several reports of renal damage after industrial exposure to Si dust (Saldanha et al. 1975, Hauglustaine et al. 1980, Giles et al. 1978).
	Assessment of uncertainty (if any)	Not done.

Publication Reference: Dobbie J. W. and Smith M. B. (1986). Urinary and serum silicon in normal and uraemic individuals. Ciba Found Symp 121: 194-213.		
Reviewer comments	Results included/excluded in review (if applicable)	• The study provides some interesting information on Si toxicokinetics but does not relate any health effects to Si exposures. Therefore, it is not considered a key study for potential guidance/guideline value development and has been excluded from further review (risk of bias analysis was also not undertaken).
	Notes on study quality, e.g. gaps, methods	

Elmore et al. 2003

Publication Reference: Elmore A. R. (2003). Final report on the safety assessment of aluminum silicate, calcium silicate, magnesium aluminum silicate, magnesium silicate, magnesium trisilicate, sodium magnesium silicate, zirconium silicate, attapulgite, bentonite, Fuller's earth, hectorite, kaolin, lithium magnesium silicate, lithium magnesium sodium silicate, montmorillonite, pyrophyllite, and zeolite. Int J Toxicol 22 Suppl 1: 37-102.		
General Information	Date of data extraction	25/05/2023
	Authors	Elmore AR (for Cosmetic Ingredient Review Expert Panel)
	Publication date	2003
	Publication type	Report / journal article / review
	Peer reviewed?	Yes
	Country of origin	USA
	Source of funding	Funding sources not specified (but likely to be the Cosmetic Ingredient Review Expert Panel, funded by the Personal Care Products Council; however, the review process is independent of the Council and cosmetics industry and the Panel operate under a set of procedures to manage potential interests) (https://www.cir-safety.org/sites/default/files/CIR%20Procedures%20-%20September%202019.pdf)
	Possible conflicts of interest	The author reports no conflicts of interest. (Members of the Panel are required to meet the same conflict of interest standards as are applicable under Federal law to special government employees).
Study characteristics	Aim/objectives of study	Report reviews the safety of aluminium, calcium, lithium magnesium, lithium magnesium sodium, magnesium aluminium, magnesium, sodium magnesium and zirconium silicates, magnesium trisilicate, attapulgite, bentonite, Fuller's Earth, Hectorite, Kaolin, Montmorillonite, Pyrophyllite and Zeolite as used in cosmetic formulations.
	Study type/design	Review
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable

Publication Reference: Elmore A. R. (2003). Final report on the safety assessment of aluminum silicate, calcium silicate, magnesium aluminum silicate, magnesium silicate, magnesium trisilicate, sodium magnesium silicate, zirconium silicate, attapulgite, bentonite, Fuller's earth, hectorite, kaolin, lithium magnesium silicate, lithium magnesium sodium silicate, montmorillonite, pyrophyllite, and zeolite. Int J Toxicol 22 Suppl 1: 37-102.		
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/ contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• The common aspect of all these claylike ingredients is that they contain silicon, oxygen, and one or more metals. • Various silicates and silicate clays are used in cosmetics, largely for their adsorbent, anticaking, bulking, and other similar properties. They are created synthetically in some cases, e.g. Lithium Magnesium Silicate, or are refined from naturally occurring minerals, e.g., Magnesium Aluminum Silicate. In either case, variations in composition occur. Thus the Zeolite group of hydrated aluminosilicates has forms that are crystalline or fibrous, and contain interchangeable cations. • Descriptions shown here have focused on subchronic and chronic oral toxicity which derived NOAELs, the types of studies which are potentially informative for guidance/guideline value derivation. • The NOAEL in a 2-year chronic oral study in Wistar rats fed synthetic zeolite A (an aluminosilicate) in their diets was the highest dose tested (58.5 mg/kg bw/d for males, 62.2 mg/kg/d for females). • Calcium silicate administered via gavage at 1,600 mg/kg (top dose) to pregnant rabbits for 13 consecutive days had no discernible effects on maternal or foetal survival or abnormalities. • Magnesium aluminium silicate (MAS) had no teratogenic effects on the mouse foetus when pregnant mice were administered up to 6,000 mg/kg/day on GD7-12. Incidences in skeletal anomalies were significantly greater in MAS-exposed foetuses, but none resulted in skeletal malformation. • Type A zeolite containing 19% silicon (15.8% sodium and 20.1% aluminium) given to rats by gavage at 1600 mg/kg on GD6-15 and rabbits at 1600 mg/kg on GD6-18 produced no adverse effects.
	How outcome was assessed	
	Method of measurement	Not applicable

Publication Reference: Elmore A. R. (2003). Final report on the safety assessment of aluminum silicate, calcium silicate, magnesium aluminum silicate, magnesium silicate, magnesium trisilicate, sodium magnesium silicate, zirconium silicate, attapulgite, bentonite, Fuller's earth, hectorite, kaolin, lithium magnesium silicate, lithium magnesium sodium silicate, montmorillonite, pyrophyllite, and zeolite. Int J Toxicol 22 Suppl 1: 37-102.		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Current concentrations of use for the various silicates considered in the review range from as low as 0.01% for Zeolite to a high of 84% for Kaolin. • The CIR Expert Panel concludes that Aluminum Silicate, Calcium Silicate, Magnesium Aluminum Silicate, Magnesium Silicate, Magnesium Trisilicate, Sodium Magnesium Silicate, Zirconium Silicate, Attapulgite, Bentonite, Fuller's Earth, Hectorite, Kaolin, Lithium Magnesium Silicate, Lithium Magnesium Sodium Silicate, Montmorillonite, Pyrophyllite, and Zeolite are safe as used in cosmetic products
	Assessment of uncertainty (if any)	• The Panel did note a concern about inhalation of these ingredients due to reported cases of pneumoconiosis and fibrosis in humans and pulmonary lesions in animals. However, extensive pulmonary damage in humans was the result of direct occupational inhalation of the dusts and lesions seen in animals were affected by particle size, fibre length, and concentration. The Panel recognises that most of the formulations are not respirable and of the preparations that are respirable, the concentration of the ingredient is very low. Even so, the Panel considered that any spray containing these solids should be formulated to minimise their inhalation.
Reviewer comments	Results included/excluded in review (if applicable)	• The review summarises a few oral toxicity studies on various silicates which provide an indication that silicates are of low subchronic and chronic oral toxicity. • The study by Gloxhuber et al. (1983) for Zeolite A provides information for a chronic 2-year study where the top dose did not result in any adverse effects (58.5 mg/kg bw/d for males, 62.2 mg/kg/d for females). Although a proportion of Zeolite A consists of hydrated silicon, but also sodium and aluminium oxides. The Gloxhuber et al. (1983) study was further assessed (see separate entry in this Appendix) and included in Risk of Bias assessment.
	Notes on study quality, e.g. gaps, methods	

Ghahramani 2010

Publication Reference: Ghahramani N. (2010). Silica nephropathy. Int J Occup Environ Med 1(3): 108-115.		
General Information	Date of data extraction	26/05/2023
	Authors	Ghahramani N
	Publication date	2010
	Publication type	Review
	Peer reviewed?	Yes
	Country of origin	USA
	Source of funding	Funding sources not specified (author is from Pennsylvania State University)
	Possible conflicts of interest	The author reports no conflicts of interest.
Study characteristics	Aim/objectives of study	Review the association between exposure to silica and various forms of kidney disease. The descriptions in this summary have focused on those exposures considered potentially relevant to the research questions (i.e. not inhalation / occupational exposures).
	Study type/design	Review
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/ contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	

Publication Reference: Ghahramani N. (2010). Silica nephropathy. Int J Occup Environ Med 1(3): 108-115.		
	How outcome was assessed	• Initial descriptions of silica nephropathy consisted mainly of sporadic case reports where silica exposure occurred via inhalation in occupational situations. • A rare but interesting possibly silicon-related syndrome presenting with painful, nodular skin lesions has been described in dialysis patients with excessively high levels of silicon (Saldanha et al. 1997). • Balkan Endemic Nephropathy is a slowly progressive chronic tubulointerstitial disease which occurs among inhabitants of villages along the Danube River in Croatia, Serbia, Romania and Bulgaria. It may occur at any age and may affect all members of the same family. The aetiology is unknown, but it is postulated to be associated with multifactorial environmental nephrotoxicity. "*In particular, chronic intoxication with drinking water polluted by silicates released during soil erosion seems to be the most probable cause*." The full-blown manifestations include co-existence of renal dysfunction with urothelial carcinoma.
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• "*Reviews of exposure-related renal disease, such as the present article, highlight the importance of a thorough occupational history in all patients with renal disease, with particular emphasis on exposure to silica, heavy metals, and solvents*."
	Assessment of uncertainty (if any)	• Authors state much further research is needed, particularly to elucidate the pathogenesis of silica nephropathy.
Reviewer comments	Results included/excluded in review (if applicable)	• The review in very general terms summarises some articles which were sourced for further analysis but provides no dose response information. • The majority of the review is focused on non-relevant routes of exposure to the research questions under consideration (i.e. occupational inhalation exposure). The review itself was therefore excluded from further assessment / review, however its bibliography was used to source additional papers.
	Notes on study quality, e.g. gaps, methods	

Gillette-Guyonnet et al. 2007

Publication Reference: Gillette Guyonnet S., Andrieu S. and Vellas B. (2007). The potential influence of silica present in drinking water on Alzheimer's disease and associated disorders. J Nutr Health Aging 11(2): 119-124.		
General Information	Date of data extraction	26/05/2023
	Authors	Gillette-Guyonnet S, Andrieu S and Vellas B
	Publication date	2007
	Publication type	Review
	Peer reviewed?	Yes
	Country of origin	France
	Source of funding	Not stated
	Possible conflicts of interest	No conflict of interest statement is included in the paper.
Study characteristics	Aim/objectives of study	To review articles published on silica present in drinking water in relation with Alzheimer's disease and associated disorders.
	Study type/design	Review
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Drinking water
	Source of chemical/ contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Alzheimer's disease and associated disorders.
	How outcome was assessed	
	Method of measurement	Review of other studies
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	

Publication Reference: Gillette Guyonnet S., Andrieu S. and Vellas B. (2007). The potential influence of silica present in drinking water on Alzheimer's disease and associated disorders. J Nutr Health Aging 11(2): 119-124.		
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• The studies reviewed by the authors of the paper suggest that high silica concentrations in drinking water may protect against impairment of cognitive function.
	Assessment of uncertainty (if any)	• Further studies are necessary to not only confirm these results but to clarify the potential effect of silica against aluminium-induced neurotoxicity and the causal role of aluminium in Alzheimer's Disease.
Reviewer comments	Results included/excluded in review (if applicable)	• This review focused on the potential ameliorative effects that silicon in drinking water may have on aluminium concentrations and neurodegenerative disorders. Although this review provides a suggestive protective effect for silicon, the authors acknowledge further studies are required. • Provides no dose response information for consideration of potential derivation of a guidance/guideline value. Excluded from further review and risk of bias analysis.
	Notes on study quality, e.g. gaps, methods	

Gitelman et al. 1992

Publication Reference: Gitelman H. J., Alderman F. R. and Perry S. J. (1992). Silicon accumulation in dialysis patients. Am J Kidney Dis 19(2): 140-143.		
General Information	Date of data extraction	26/05/2023
	Authors	Gitelman HJ, Alderman FR, Perry SJ
	Publication date	1992
	Publication type	Human study (observations in dialysis patients)
	Peer reviewed?	Yes
	Country of origin	USA
	Source of funding	Supported in part by Whitby Research Inc
	Possible conflicts of interest	No conflict of interest statement is included in the paper.
Study characteristics	Aim/objectives of study	Study obtained plasma silicon measurements in patients with end-stage renal disease on chronic dialysis therapy
	Study type/design	Human study (observations in dialysis patients)
	Study duration	On dialysis for at least 2 months.
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	All patients studies were being treated at the North Carolina Memorial Hospital or one of its satellite dialysis centres. All patients had been on chronic therapy for at least 2 months.
	Selection criteria for population (if applicable)	

Publication Reference: Gitelman H. J., Alderman F. R. and Perry S. J. (1992). Silicon accumulation in dialysis patients. Am J Kidney Dis 19(2): 140-143.		
	Subgroups reported	1) Haemodialysis, in-centre: n=26 2) Haemodialysis, satellite: n=7 3) Peritoneal dialysis: n=25
	Size of study	N=58 patients
Exposure and setting	Exposure pathway	Dialysis fluid
	Source of chemical/ contamination	Tap water (for preparation of dialysis fluid) with or without reverse osmosis treatment or (for peritoneal dialysis) it was commercially available peritoneal dialysis fluid.
	Exposure concentrations (if applicable)	1) Haemodialysis, in-centre: 4.0 ± 0.7 mg Si/L in dialysis fluid 2) Haemodialysis, satellite: 0.5 ± 0.4 mg Si/L in dialysis fluid 3) Peritoneal dialysis: 0 ± 0.1 mg Si/L in dialysis fluid
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not stated (only plasma Si analytical method is provided)
	Water sampling methods (monitoring, surrogates)	Not stated
Results (for each outcome)	Definition of outcome	• All patients on dialysis had plasma silicon values that were significantly higher than normal. In-centre haemodialysis patients showed the highest values (4.6 ± 0.4 mg Si/L) with less in the satellite group (2.5 ± 0.2 mg Si/L) and the peritoneal dialysis group (1.9 ± 1.2 mg/L). • The in-centre haemodialysis patients were being dialysed with dialysis fluids containing two different concentrations of silicon. A central reverse osmosis system provided dialysis fluid containing 5.2 ± 0.2 mg/L silicon to 8 of 11 stations; the others deliver 0.3 mg/L silicon. • Authors reviewed the medical records of the 58 study patients to determine whether plasma silicon concentrations could be correlated with general health or available clinical data.
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable

Publication Reference: Gitelman H. J., Alderman F. R. and Perry S. J. (1992). Silicon accumulation in dialysis patients. Am J Kidney Dis 19(2): 140-143.		
Author's conclusions	Interpretation of results	• Authors found no obvious deleterious effect of plasma silicon elevation on overall health of patients. There was no consistent relationship between plasma silicon levels and age, duration of dialysis, blood urea nitrogen, serum creatinine, serum calcium, serum phosphate, use of aluminium-containing antacid medication or serum aluminium levels. Additionally, they found no evidence of an interaction between silicon and bone metabolism. • Silicon content of drinking water is one factor that contributed to large within-group variability. • Authors indicate the data confirm the presence of increases in the concentration of silicon in plasma in individuals with end-stage renal disease on dialysis therapy.
	Assessment of uncertainty (if any)	• It is conceivable that the concurrent exposure of the authors' dialysis patients to high levels of silicon may have contributed to an apparent lack of aluminium toxicity. This possibility merits further evaluation.
Reviewer comments	Results included/excluded in review (if applicable)	• This study shows that exposure to silicon in dialysis fluids can increase silicon levels in plasma. It suggests no overt adverse health effects from silicon exposure in dialysis fluid in end-stage renal disease but is obviously limited by the limited endpoints examined. • As the study does not provide dose response information for potential derivation of a guidance/guideline value for drinking water, it was not subjected to risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

Gloxhuber et al. 1983

Publication Reference: Gloxhuber Ch, Potokar M, Pitterman W, Wallat S, Bartnik F, Reuter H, Braig S (1983). Zeolithe A – A phosphate substitute for detergents: toxicological investigation. Food and Chemical Toxicology. 21(2): 209-220.		
General Information	Date of data extraction	27/06/2023
	Authors	Gloxhuber Ch, Potokar M, Pitterman W, Wallat S, Bartnik F, Reuter H, Braig S
	Publication date	1983
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Germany
	Source of funding	Funding sources not specified (author is from Henkel, a Chemical Company)
	Possible conflicts of interest	No conflict of interest statement included in the paper.
Study characteristics	Aim/objectives of study	To investigate the safety of exposure to Zeolithe A, a sodium aluminium silicate developed as a substitute for phosphates in detergents.

Publication Reference: Gloxhuber Ch, Potokar M, Pitterman W, Wallat S, Bartnik F, Reuter H, Braig S (1983). Zeolithe A – A phosphate substitute for detergents: toxicological investigation. Food and Chemical Toxicology. 21(2): 209-220.		
	Study type/design	Experimental animal studies (only results from oral studies were included in this data extraction).
	Study duration	• Acute oral toxicity: Single dose, 8-day observation • Subchronic oral toxicity: 90 days • Chronic toxicity/carcinogenicity: 104 weeks (2 years)
	Type of water source (if applicable)	Tap water (*ad libitum*)
Population characteristics	Population/s studied	• Acute oral toxicity: 10 male Wistar rats (180g bw) • Subchronic oral toxicity: Wistar rats (20/sex/group) (150g bw in males, 140g in females). • Chronic toxicity/carcinogenicity: Wistar rats (50/sex/group) and satellite groups of 15/sex
	Selection criteria for population (if applicable)	
	Subgroups reported	• Acute oral toxicity: Not applicable • Subchronic oral toxicity: 5 groups (20/sex/group) • Chronic toxicity/carcinogenicity: 4 groups (50/sex/group) and satellite groups of 15/sex (providing samples for initial and interim investigations)
	Size of study	See above
Exposure and setting	Exposure pathway	• Acute oral toxicity: Oral (Gavage in aqueous suspension of 10g Zeolithe A/kg) • Subchronic oral toxicity: Oral (in diet) • Chronic toxicity/carcinogenicity: Oral (in diet)
	Source of chemical/ contamination	Zeolithe A, a sodium aluminium silicate with the formula $Na_{12}(AlO_2)_{12}(SiO_2)_{12}$ x $27H_20$. Consists of cubic microcrystals with an average particle diameter of 10 µm which agglomerate to form bigger particles and may disintegrate in water. Batches used ranges in diameter from 6.1-9.3 µm.
	Exposure concentrations (if applicable)	• Acute oral toxicity: 10g Zeolithe A/kg • Subchronic oral toxicity: 0, 1000, 5000, or 10,000 ppm Zeolithe A in diet • Chronic toxicity/carcinogenicity: 0, 10, 100, or 1000 ppm Zeolithe A in diet.
	Comparison group(s)	Control groups received untreated diet in the repeat exposure studies.
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• Acute oral toxicity: Mortality

Publication Reference: Gloxhuber Ch, Potokar M, Pitterman W, Wallat S, Bartnik F, Reuter H, Braig S (1983). Zeolithe A – A phosphate substitute for detergents: toxicological investigation. Food and Chemical Toxicology. 21(2): 209-220.		
	How outcome was assessed	• Subchronic oral toxicity: Body weights and food consumption estimated at weekly intervals. At the end of 90-day period, urine samples from still surviving test and control animals were examined for volume, pH, protein, glucose, urobilinogen, ketones, specific gravity, blood and spun deposit, and blood samples were taken for haemoglobin determinations, red cell and total white cell counts and determination of blood sugar, serum alkaline phosphatase, serum glutamic pyruvic transaminase, serum glutamic-oxalacetic transaminase, urea and total serum proteins. The animals were killed, organ weights (including those of the brain, heart, kidney, liver, gonads, adrenal glands, thyroid gland, pituitary gland and thymus) were recorded and 20 different organs were subjected to histological examination. Additionally, the iron concentration of the blood, the concentration of copper and cobalt in the liver and the concentrations of zinc, aluminium, copper and silicon in the kidney were determined. • Chronic toxicity/carcinogenicity: Mortality, morbidity, feed and water intake and body weights were recorded. After 6, 26, 78 and 104 weeks, red and white (total and differential) blood cell and thrombocyte counts were performed, and haematocrits, haemoglobin and clotting times were determined. Urinary volume, pH, protein, urobilinogen, ketones, blood and aluminium and silicon in the spun deposit were determined. In addition to the standard biochemical evaluations, iron, cobalt and copper in the liver, and zinc and aluminium and silicon in the kidney were determined at weeks 78 and 104. Autopsy of the satellite groups was performed after 78 weeks and of the main groups after 104 weeks. About 36 organs from ten males and ten females of the control and 1000 ppm groups were examined histologically together with all tumour tissues (actual or suspected) in the controls and all test groups.
	Method of measurement	Various publications cited for method of measurement of metals in urine and tissues.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	• Subchronic oral toxicity: Control group 20/sex (exposed groups also 20/sex/group) • Chronic toxicity/carcinogenicity: Control group (50/sex + satellite group of 15/sex)
Statistics (if any)	Statistical method used	Details not provided in study methods. Comparison of the separate sums of the tumorous changes observed in the 1000 ppm Zeolithe A and control groups was done by the statistical method of Kastenbaum & Bowman (1970).
	Details on statistical analysis	

	Relative risk/odds ratio, confidence interval?	Not applicable. Summary of results: • Acute oral toxicity: Rats tolerate a single oral dose of 10g Zeolithe A/kg bw without any overt adverse reactions. • Subchronic oral toxicity: All the experimental rats survived. The only differences between test and control groups were found in the group fed the highest dose of Zeolithe A (10,000ppm). This group showed diminished urine secretion, haematuria and ketone bodies in the urine and in 12 of the 20 male animals urinary calculi of varying number and size were observed in the bladder, as well as a thickening of the wall. The histological examination showed a hyperplastic reaction of the transitional epithelium in rats with calculi. None of the elements determined showed any significant differences between the experimental groups and the controls, apart from the silicon content of the kidneys, which was considerably higher than in the controls (Control males 528 ± 99 µg/g kidney vs. 1,688 ± 1,021 µg/g kidney in treatment group), especially in the males of the group fed the highest dietary level. • Chronic toxicity/carcinogenicity: Zeolithe A intake was calculated as 0.62 and 0.65 mg/kg/day for males and females, respectively, fed the dietary level of 10ppm, as 6.10 and 6.53 mg/kg/day for those fed 100ppm and as 58.47 and 62.15 mg/kg/day for those fed 1000ppm. During the test period of 104 weeks, the numbers (total deaths and, in parenthesis, those not autopsied because of autolysis) of male rats that died or had to be killed because of their condition were 18 (5), 8 (4), 13 (5) and 7 (2) in the groups fed 0, 10, 100 and 1000ppm Zeolithe A, respectively. The corresponding female figures were 8 (1), 17 (2), 15 (2) and 17 (5). The body weights of the male satellite test groups corresponded to those of the controls. In the females, the body weights in all these three test groups were significantly lower ($P < 0.05$) than those of the controls from week 12 onwards. In the main groups, however, no difference in body-weight gain was observed between controls and experimental animals. The number of leukocytes was decreased in male rats of the 1000ppm group, but this was not considered to be due to treatment by study authors. Differential blood cell and bone marrow cell counts showed no significant differences between test and control animals. Neither did albumin and globulin. The excretion of Si and Al via urine was slightly greater in 1000ppm test animals compared to controls but was not statistically significant. Organ weights of male animals showed no significant differences when compared to control values. In the females, relative weights of the adrenal glands of the 10ppm group and thymus of 100 and 1000 ppm groups differed significantly ($p<0.05$) from controls. In animals dying during the test or killed because of their poor condition, the main causes were basophilic adenoma and adenocarcinoma of the pituitary gland, adenoma and fibroadenoma of the mammary glands, subcutaneous fibroma and some tumours of the genital tract. No significant incidence of a particular type of tumour or of spontaneous mortality was evident in any group. No treatment-related findings were seen in any of the organs examined histologically, and there was no indication of any

Publication Reference: Gloxhuber Ch, Potokar M, Pitterman W, Wallat S, Bartnik F, Reuter H, Braig S (1983). Zeolithe A – A phosphate substitute for detergents: toxicological investigation. Food and Chemical Toxicology. 21(2): 209-220.		
		treatment- related reduction of neoplasms. Comparison of the separate sums of the tumorous changes observed in the 1000ppm Zeolithe A and control groups by the statistical method of Kastenbaum & Bowman (1970) showed no significant difference between the groups in the frequency of tumours.
Author's conclusions	Interpretation of results	• Zeolithe A showed only slight acute, subchronic and chronic toxicity. • The safety of the possible uptake of traces of Zeolithe A was tested in a 2-year study, in which 10, 100 and 1000 ppm was fed to rats. The results did not indicate any carcinogenic activity. • In the subchronic feeding study, bladder calculi occurred in male rats fed 10,000ppm Zeolithe A. This, together with the chemical assays performed, proved that Zeolithe A was absorbed to a small extent after ingestion. The absorption is presumed to take place only after dissociation of the Zeolithe A molecule, since the silicon component but not the aluminium could be traced in the urine. The aluminium in the molecule, therefore, seems not to be absorbed to any significant extent. The absorption of Zeolithe A after ingestion was estimated to be about 1%.
	Assessment of uncertainty (if any)	Not done
Reviewer comments	Results included/excluded in review (if applicable)	• This study indicates there were no treatment-related adverse effects observed in a 2-year study in which rats were fed up to 1,000 ppm Zeolithe A (an aluminosilicate). This corresponds to a dose of 58.47 mg/kg/d in males and 62.15 mg/kg/d in females. • Si content, based on molecular formula is ~15%, which suggests a chronic NOAEL of 8.8 mg/kg/d in males and 9.3 mg/kg/d in females for the Si content in Zeolithe A may be applicable. • Since this study potentially provides dose response information for Si, it was subjected to RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Gordova et al. 2015

Publication Reference: Gordova V. S., Dyachkova I. M., Sergeeva V. E., Sapozhnikov S. P. and Smorodchenko A. T. (2015). Morphofunctional adaptation of rat thymus structures to silicon consumption with drinking water. Bull Exp Biol Med 158(6): 816-819.		
General Information	Date of data extraction	26/05/2023
	Authors	Gordova VS, Dyachkova IM, Sergeeva VE, Sapozhnikov SP, Smorodchenko AT

Publication Reference: Gordova V. S., Dyachkova I. M., Sergeeva V. E., Sapozhnikov S. P. and Smorodchenko A. T. (2015). Morphofunctional adaptation of rat thymus structures to silicon consumption with drinking water. Bull Exp Biol Med 158(6): 816-819.		
	Publication date	2015
	Publication type	Experimental animal study
	Peer reviewed?	Yes
	Country of origin	Russia and Germany
	Source of funding	Not stated
	Possible conflicts of interest	No conflict of interest statement is included in the paper.
Study characteristics	Aim/objectives of study	To study the morphofunctional state of the thymus after exposure to silicon in drinking water of rats.
	Study type/design	Experimental animal study
	Study duration	2 months
	Type of water source (if applicable)	Drinking Sestritsa-Prirodnaya water
Population characteristics	Population/s studied	White outbred male rats (150-200g)
	Selection criteria for population (if applicable)	
	Subgroups reported	1) Control (n=40) received *ad libitum* drinking Sestritsa-Prirodnaya water 2) Experimental group (n=30) received *ad libitum* drinking Sestritsa-Prirodnaya water containing sodium metasilicate (10 mg Si/L) (i.e. 0.4-0.6 mg Si/kg bw/d)
	Size of study	N=70 animals
Exposure and setting	Exposure pathway	Drinking water (*ad libitum*)
	Source of chemical/ contamination	In treatment group, sodium metasilicate was added at a concentration of 10 mg Si/L
	Exposure concentrations (if applicable)	0 (presumed, but not confirmed in study) or 10 mg Si/L
	Comparison group(s)	Controls
Study methods	Water quality measurement used	-
	Water sampling methods (monitoring, surrogates)	-
Results (for each outcome)	Definition of outcome	• Thymus was isolated immediately after sacrifice and embedded in paraffin. Paraffin sections were stained using routine morphological and immunohistochemical methods. • The mean areas of the cortex and medulla were 1.07±0.14 and 0.28±0.10 mm^2, while the corresponding values in the control group were 0.88±0.11 and 0.25±0.04 mm^2. In the experimental group, thymocyte number per unit area (0.04 mm^2) was significantly ($p<0.05$) higher than in the control group (145.6 vs. 122.8 in the medulla; 93.4 vs. 73.6 in the cortex). Size of thymocytes considerably changed in animals treated with silicon.
	How outcome was assessed	

Publication Reference: Gordova V. S., Dyachkova I. M., Sergeeva V. E., Sapozhnikov S. P. and Smorodchenko A. T. (2015). Morphofunctional adaptation of rat thymus structures to silicon consumption with drinking water. Bull Exp Biol Med 158(6): 816-819.		
	Method of measurement	Antigen-presenting cells (APC) in the thymus (dendritic cells and phagocyting macrophages) were detected by immunohistochemical method of indirect enzyme-linked immunoassay (ELISA) using antibodies against major histocompatibility complex Class II antigens (MHC-II); monocyte-macrophage cells were detected using antibodies against calcium-binding adapter molecule (Iba-1).
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	40 non-exposed, 30 exposed animals
Statistics (if any)	Statistical method used	Sigma deviation (σ) and standard error of the mean (M) were calculated for all means. The cells were ranked according to their size taking into account the sigma deviations: M±σ were regarded as middle-sized cells, >M+σ, as large cells, <M-σ, as small cells. Significance of differences ($p \leq 0.05$) between the means (Student's t test) was calculated at "tails"=2 (two-way distribution), type=1 (paired samples).
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Authors indicate their experiments have shown that silicon from drinking water has a definite influence on the redistribution and morphology of thymic cells of the monocyte-macrophage origin. • Structures responsible for maturation of T lymphocytes are probably the target for the water-soluble silicon compounds, and changes occurring in them may create preconditions for the development of diseases associated with autoreactivity.
	Assessment of uncertainty (if any)	• Changes in cells of the monocyte-macrophage origin in the cortex may suggest enhanced metabolic activity (increased size) and functional activity (reduced cytoplasmic Iba-1 protein) in response to a decrease in their number. Since macrophages in the cortex form complexes with immature T lymphocytes and promote their maturation and differentiation, the increase in their area is a possible functional and compensatory response to a decrease in their number.
Reviewer comments	Results included/excluded in review (if applicable)	• Animal study with administration of a single dose (where dose is cited, but no measurement of silicon in control water appears to have been undertaken) which examined cellular changes in the thymus of rats. It is unclear if these changes (many of which were not significantly different from the control group) translate to adverse effects. • As the study is not considered to provide useful dose response information (due to lack of more than one dose and due to lack of clear adversity of the effects observed), it was not included for further assessment or further risk of bias analysis.
	Notes on study quality, e.g. gaps, methods	

Hagman et al. 2020

Publication Reference: Hagman E., Elimam A., Kupferschmidt N., Ekbom K., Rössner S., Iqbal M. N., Johnston E., Lindgren M., Bengtsson T. and Danielsson P. (2020). Oral intake of mesoporous silica is safe and well tolerated in male humans. PLoS One 15(10): e0240030.		
General Information	Date of data extraction	26/05/2023
	Authors	Hagman E, Elimam A, Kupferschmidt N, Ekbom K, Rössner S, Iqbal MN, Johnston E, Lundgren M, Bengtsson T, Danielsson P
	Publication date	2020
	Publication type	Human Controlled Trial
	Peer reviewed?	Yes
	Country of origin	Sweden
	Source of funding	This study was supported by Sigrid Therapeutics AB https://www.sigridthx.com/. The company provided the compound studied and sponsored Division of paediatrics, CLINTEC, Karolinska Institutet to conduct the study and external companies for analysing urine. Sigrid Therapeutics AB was partly involved in the study design and manuscript preparation but were not involved in data collection, data analysis or decision to publish. Sigrid Therapeutics AB also provided some support in the form of salaries or other form of remuneration at the time of the study for authors NK, SR, EJ, ML, MNI and TB.
	Possible conflicts of interest	The following authors have the following competing interests: NK, SR, EJ, ML, MNI and TB are or have been connected to Sigrid Therapeutics AB (employed, consultant or advisory board). This commercial affiliation does not alter their adherence to PLOS ONE policies on sharing data material. EH, AE, KE, and PD declared that no competing interests exist.
Study characteristics	Aim/objectives of study	To determine whether oral dosing, up to 9 grams/day, of precisely engineered mesoporous silica as a food additive can be used safely in male humans.
	Study type/design	Single Blinded Uncontrolled First-In-Man study with a placebo run-in period
	Study duration	3 times/day for 21 days for normal weight individuals (including a 5-day placebo run-in period), continued an additional 10 weeks for obese individuals.
	Type of water source (if applicable)	Not stated

Publication Reference: Hagman E., Elimam A., Kupferschmidt N., Ekbom K., Rössner S., Iqbal M. N., Johnston E., Lindgren M., Bengtsson T. and Danielsson P. (2020). Oral intake of mesoporous silica is safe and well tolerated in male humans. PLoS One 15(10): e0240030.		
Population characteristics	Population/s studied	Two study arms including 10 young (18-35 years) males each. One arm consisted of normal weight participants with BMI ranges between 20.0–25.0 kg/m^2 and one arm with participants with obesity, BMI ranges between 30.0–45.0 kg/m^2. All included subjects were recruited via advertisement, and the study was performed August 17th to December 21st 2015 in Stockholm, Sweden. Exclusion criteria for both study arms included; chronic somatic diseases that may affect metabolic and/or gastro-intestinal function (e.g. diabetes, hypertension, dyslipidemia, inflammatory bowel disease, gluten intolerance, pancreatic dysfunction, other causes of malabsorption, neoplastic disease), allergies with previous anaphylactic reactions, previous abdominal surgery, and current or previous history of eating disorders. Further exclusion criteria include; restrictive diets (e.g. very low carbohydrate or vegan) during the past year, psychiatric disorders that may influence adherence (e.g. schizophrenia), drug or alcohol abuse, continuous pharmacological treatment that might influence the study outcome, and other conditions which the investigator considered could negatively affect the outcome of the study or study adherence.
	Selection criteria for population (if applicable)	
	Subgroups reported	Two groups (normal weight allocated to intervention or non-normal weight allocated to intervention) (n=10/group)
	Size of study	N=20
Exposure and setting	Exposure pathway	Drinking water
	Source of chemical/ contamination	Precisely engineered mesoporous silica compounds were synthesized by a modified method. The silica was delivered to participants as powder in vials containing 1.0–3.0 grams of the silica per portion to be mixed with water in each powder containing vial. The participants were instructed to drink a large glass (approximately 250 mL) of water with the powder.
	Exposure concentrations (if applicable)	0-9 g/day (i.e. ~0-0.11g/kg bw/d in healthy weight individuals, 0.08 g/kg bw/d in obese individuals).
	Comparison group(s)	Cellulose powder (VIVAPUR1 MCC Microcrystalline cellulose) was used as placebo and provided in identical looking placebo vials. The placebo was given blinded i.e. single blinded in that the healthy volunteers were not informed about the placebo run-in.
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Silica concentration, measured as silicon content, in urine was measured with ICP-SFMS by ALS Scandinavia AB, Luleå, Sweden.
Results (for each outcome)	Definition of outcome	

Publication Reference: Hagman E., Elimam A., Kupferschmidt N., Ekbom K., Rössner S., Iqbal M. N., Johnston E., Lindgren M., Bengtsson T. and Danielsson P. (2020). Oral intake of mesoporous silica is safe and well tolerated in male humans. PLoS One 15(10): e0240030.		
	How outcome was assessed	• An experienced registered nurse performed the measurements of weight, height, and blood pressure manually. A medical doctor performed cardio-respiratory and abdominal examinations. At baseline a food frequency questionnaire (FFQ) was obtained. At all visits questions regarding adherence, lifestyle changes, gastrointestinal function/habits and adverse events were asked and answered. Fasting blood samples and faeces was also collected. • No changes noted with regards to body weight, BMI or blood pressure. No consistent pattern of change in eating patterns or physical activity. • Although erythrocytes, haemoglobin and erythrocyte volume fraction (EVF) showed statistically significant reductions during Phase 1 in normal weight participants, the changes observed are within normal range and show no signal for safety concerns. • The creatinine levels were unchanged in the arm with normal weight participants (p = 0.37). Among the obese participants, the creatinine levels decreased from baseline (84.0 µmol/L) to Phase 2 follow-up (76.0 µmol/L), (p = 0.025), resulting in a normalisation of all participants' creatinine values. On an average level, cystatin C and eGFR remain unchanged for both arms. However, one participant with obesity had a slightly elevated creatinine level at baseline (106 µmol/L) and increased his cystatin C level to an abnormal level for his age (1.31 mg/L) by the end of Phase 2. Calculated eGRF based on different methods at the end of Phase 2 showed however large differences; eGFR based on cystatin C was 57 ml/min/1.73 m^2 whereas eGFR based on creatinine was 87.4. This participant was followed up with further investigations of his kidneys (iohexol clearance test) at five months post the end of Phase 2, and the kidney function showed normal activity. The baseline values might indicate that impaired or fluctuating kidney function could already have been present at study initiation.
	Method of measurement	See above
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	N=20 (all exposed, with their own placebo run-in period) Zero missing/excluded
Statistics (if any)	Statistical method used	Descriptive statistics are presented with mean-, min- and max values. To investigate differences in anthropometrical measures and biomarkers from baseline to follow-up visits, paired t-tests were used to assess differences in anthropometrical measures and biomarkers from baseline to follow-up visits. Only reported values were used for the purpose of these analyses, i.e. no data were imputed. All analyses were performed in STATISTICA.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable

Publication Reference: Hagman E., Elimam A., Kupferschmidt N., Ekbom K., Rössner S., Iqbal M. N., Johnston E., Lindgren M., Bengtsson T. and Danielsson P. (2020). Oral intake of mesoporous silica is safe and well tolerated in male humans. PLoS One 15(10): e0240030.		
Author's conclusions	Interpretation of results	• In this safety study, an oral intake of up to 9 grams per day of porous silica can be consumed without any major adverse events or safety concerns. • None of the study participants reported any changes in diet, physical activity or sleep patterns during the study period as reported in the follow-up questions at each visit.
	Assessment of uncertainty (if any)	• Data from this relatively small safety study should interpreted with care and monitoring the levels of both vitamins and trace elements as well as kidney function should be considered in further trials. However, even if some biomarkers changed during this trial, these changes were of no or minor clinical relevance and adverse events observed were mild, transient and did not result in discontinuation, dose reduction or safety concern. Therefore, the authors conclude, in line with public data on food grade silica, that also engineered synthetic porous silica is safe to consume in relatively high doses in male humans.
Reviewer comments	Results included/excluded in review (if applicable)	• Although a limited number of endpoints were monitored, this study suggests that an oral dose of 110 mg Si/kg bw/d (as mesoporous silica) for 16 days (excluding placebo period) in healthy weight individuals and 80 mg Si/kg bw/d for ~12 weeks does not result in any overt adverse health effects in male humans. • As the study may provide useful dose response information, it was subjected to a risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

Hao et al. 2022

Publication Reference: Hao P., Wang Y., Sun X., Wang J. and Zhang L. W. (2022). Derivation of the toxicological threshold of silicon element in the extractables and leachables from the pharmaceutical packaging and process components. Toxicol Ind Health 38(12): 819-834.		
General Information	Date of data extraction	26/05/2023
	Authors	Hao P, Wang Y, Sun X, Wang J, Zhang LW
	Publication date	2022
	Publication type	Review
	Peer reviewed?	Yes
	Country of origin	China
	Source of funding	The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Natural Science Foundation of China.
	Possible conflicts of interest	The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Publication Reference: Hao P., Wang Y., Sun X., Wang J. and Zhang L. W. (2022). Derivation of the toxicological threshold of silicon element in the extractables and leachables from the pharmaceutical packaging and process components. Toxicol Ind Health 38(12): 819-834.		
Study characteristics	Aim/objectives of study	Review and evaluate toxicological thresholds of silicon because of its direct contact with drug products especially a liquid form of drug products with the widely used pharmaceutical packaging systems made of silicon materials like glass and silicone. Only data for the oral route of exposure has been summarised below as this is relevant to the research questions.
	Study type/design	Review
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	A thorough literature search was performed on Google, Google scholar, and Web of Science using the keywords or their combinations as follows: pharmaceutical, toxicity, toxicological risk assessment, intravenous, inhalation, oral, in vivo, in vitro; crystal, amorphous, colloidal, inorganic silicon, silica, silicon dioxide, glass, ampoules, particles, shedding, delamination; silicone elastomer, silicone fluid, silicone oil, tubing, polydimethylsiloxane, oligomers, siloxanes.
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/ contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• Elemental Si is commonly regarded as a virtually safe element by the vast majority when exposed orally in our daily life.

Publication Reference: Hao P., Wang Y., Sun X., Wang J. and Zhang L. W. (2022). Derivation of the toxicological threshold of silicon element in the extractables and leachables from the pharmaceutical packaging and process components. Toxicol Ind Health 38(12): 819-834.		
	How outcome was assessed	• The toxicity of silicon for the parenteral route of administration has not been reviewed. It is necessary to set a parenteral permitted daily exposure (PDE) value for silicon to supplement ICH Q3D (ICH Q3D, 2019) and European Medicines Agency (EMA) metal catalyst and reagent guide (EMA 2008, as cited in Hao et al. 2022). • In a 2-year mouse and rat oral study of silica gel (amorphous silica) with doses up to 10,000 mg/kg and 2500 mg/kg, respectively, no significant dose-related effects were seen at any dose level (ECHA registered-dossier, silicon). The authors derived PDEs of 1,944 mg/d and 1,167 mg/d for humans from this study. • In another study, 110 nm silica nanoparticles administered orally (timeframe not stated) to rats gave a NOAEL of 5,000 mg/kg bw/d. The authors derived a PDE of 18,919 µg Si/day from this study.
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• The oral toxicity of silica is very low. There is no difference in the toxicity of crystalline and non-crystalline silica reported. Therefore, the PDE value of oral inorganic Si is 18,919 µg/day, suitable for inorganic silicon exposure, mostly amorphous silica, in pharmaceutical packaging, and process components.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• The review provides some useful data for what appears to be a proprietary oral 2-year study on amorphous silica in mice and rats. NOAEL of 2,500 mg/kg bw/d obtained in mice. Unfortunately, the original reference is not provided in the paper, but this may be referring to the Takizawa et al. (1988) study (reviewed as part of the search). • Authors present a PDE for oral inorganic Si of 18,919 µg/day. At a 70 kg body weight for an Australian adult, this converts to 270 µg/kg/d (i.e. 0.27 mg/kg/d). Note this is based on a study in silica nanoparticles which is likely not applicable to the exposure circumstances for silicon brasses.
	Notes on study quality, e.g. gaps, methods	

Hershey et al. 1983

Publication Reference: Hershey C. O., Ricanati E. S., Hershey L. A., Varnes A. W., Lavin P. J. and Strain W. H. (1983). Silicon as a potential uremic neurotoxin: trace element analysis in patients with renal failure. Neurology 33(6): 786-789.		
General Information	Date of data extraction	27/05/2023
	Authors	Hershey CO, Ricanti ES, Hershey LA, Varnes AW, Lavin PJM, Strain WH
	Publication date	1983
	Publication type	Retrospective human observational study / case study
	Peer reviewed?	Yes
	Country of origin	USA
	Source of funding	Funding received from Frackelton Memorial Fund and the Andrew W. Mellon Foundation.
	Possible conflicts of interest	No conflict of interest statement was included in the paper.
Study characteristics	Aim/objectives of study	Doctors experienced an epidemic of dialysis dementia among patients attending a dialysis centre studied the patients to determine whether trace elements in cerebrospinal fluid (CSF) and dialysis fluids were abnormal.
	Study type/design	Human observational study / case study
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Four groups of patients selected from Jan 1981-Nov 1981: 1) N=9 on dialysis (2 on peritoneal, others on haemodialysis). 3 heomodialysed patients had dialysis dementia (mean age = 59 years) 2) Controls 1 (n=18): with no dialysis dementia (although symptoms had prompted neurologic investigation, no specific disease was found (mean age = 39 years). No renal impairment. 3) Controls 2 (n=12): Patients with Parkinson's disease, normal-pressure hydrocephalus, and alcoholic dementia (mean age = 73 years). No renal impairment. 4) Patients with renal impairment who were not dialysed and who were not demented. Patients with Alzheimer's disease and metabolic disorders (e.g. hepatic encephalopathy, diabetic ketoacidosis or hyperosmolar coma) were excluded.
	Selection criteria for population (if applicable)	
	Subgroups reported	See above
	Size of study	See above
Exposure and setting	Exposure pathway	Dialysis fluid
	Source of chemical/ contamination	Tap water
	Exposure concentrations (if applicable)	See below

Publication Reference: Hershey C. O., Ricanati E. S., Hershey L. A., Varnes A. W., Lavin P. J. and Strain W. H. (1983). Silicon as a potential uremic neurotoxin: trace element analysis in patients with renal failure. Neurology 33(6): 786-789.		
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Inductively coupled argon plasma emissions spectrometry (LOR: 0.03 mg/L for Si)
	Water sampling methods (monitoring, surrogates)	In March 1981, dialysate was analysed. Bath was a standard commercial dialysis concentrate, diluted with water from the city water supply. Authors collected samples of tap water, dialysis bath and dialysate from the exit coils where the fluid interfaces with the patient. They also examined dialysis concentrate after dilution with deionised water. In June 1981, a deioniser was operational in the dialysis unit and the analysis was repeated.
Results (for each outcome)	Definition of outcome	• CSF was collected after informed consent. • In March 1981, dialysate had significant amounts of Al, Ba, Cu, Si, and Zn at levels identical to those in tap water. Concentrations of Al, Ba, Cu, and Zn significantly decreased after interface with the patients, but Si concentrations increased. • Si concentration (n=5) before deioniser was 0.349 mg/L in bath, 0.427 mg/L post-patient. After deioniser (n=7) it was <0.03 mg/L in bath and 0.077 mg/L post-patient. • CSF silicon was significantly higher in dialysis patients than in either of the control groups (p<0.025). • CSF silicon did not correlate with present or absence of dialysis dementia. Authors also found elevated CSF silicon in patients with chronic renal insufficiency who were not being dialysed. CSF silicon increased as renal function declined.
	How outcome was assessed	
	Method of measurement	Not stated
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	See above
Statistics (if any)	Statistical method used	Statistical methods included the two-tailed student t test and linear regression analysis.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• According to authors: "*If silicon is nephrotoxic, and if it accumulates in body tissues in patients with renal failure as suggested by our CSF findings, it may contribute to the steady progression of renal failure once initiated*." • Silicon may be a neurotoxin. Because the level of silicon did not correlate with dialysis dementia, and because authors found elevated CSF silicon in renal failure patients who were not on dialysis, silicon may not be the sole cause of dialysis dementia.
	Assessment of uncertainty (if any)	CSF silicon concentrations 20 times control values do not prove toxicity. The element may be inert. Nevertheless, the presence of silicon in the drinking water, dialysis fluids, and CSF of dialysis and renal failure patients requires that silicon be considered for a role in dialysis dementia and the neurotoxicity of uraemia.

Publication Reference: Hershey C. O., Ricanati E. S., Hershey L. A., Varnes A. W., Lavin P. J. and Strain W. H. (1983). Silicon as a potential uremic neurotoxin: trace element analysis in patients with renal failure. Neurology 33(6): 786-789.		
Reviewer comments	Results included/excluded in review (if applicable)	• This study did not find correlation between silicon levels in CSF and dialysis dementia, which suggests silicon may not be the cause of dialysis dementia. • The authors' conclusions may be premature as this study examined only a small number of variables targeted to metal/elemental causes. • The study does not provide dose response information for Si, therefore it was excluded from further assessment or risk of bias analysis.
	Notes on study quality, e.g. gaps, methods	

Jacqmin-Gadda et al. 1996

Publication Reference: Jacqmin-Gadda H., Commenges D., Letenneur L. and Dartigues J. F. (1996). Silica and aluminum in drinking water and cognitive impairment in the elderly. Epidemiology 7(3): 281-285.		
General Information	Date of data extraction	27/05/2023
	Authors	Jacqmin-Gadda H, Commenges D, Letenneur L, Dartigues J-F
	Publication date	1996
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	France
	Source of funding	This research was supported by the Fondation de France, Paris, France; Sandoz Laboratories, Paris, France; Pechiney, Paris, France; Danone, Paris, France; Axa Insurance Group, Paris, France; the Conseil General de la Dordogne; the Ministere de la Recherche et de la Technologie; the Caisse Nationale d'Assurance Maladie; the Caisse Primaire d'Assurance Maladie de Dordogne; the Mutualite Sociale Agricole de Gironde et Dordogne; the Conseil Regional d'Aquitaine; 2010 Media, Paris, France; Capimmec; and the Direction Regionale des Affaires Sanitaires et Sociales d'Aquitaine. The work of Helene Jacqmin-Gadda was supported by the Recherche et Partage Association.
	Possible conflicts of interest	No conflict of interest statement was included in the paper.
Study characteristics	Aim/objectives of study	To study the relationship between silica and aluminium levels in drinking water and the risk of cognitive impairment in France.
	Study type/design	Cross-sectional study
	Study duration	Not applicable
	Type of water source (if applicable)	Not stated (drinking water)
	Population/s studied	

Publication Reference: Jacqmin-Gadda H., Commenges D., Letenneur L. and Dartigues J. F. (1996). Silica and aluminum in drinking water and cognitive impairment in the elderly. Epidemiology 7(3): 281-285.		
Population characteristics	Selection criteria for population (if applicable)	Paquid study which comprises 3,777 subjects age 65 years and older living at home in 75 civil parishes of Gironde and Dordogne in southwestern France. Samples were randomly selected from electoral rolls by a three-step procedure with stratification by age, sex, and size of urban unit.
	Subgroups reported	Exposures divided into different cut-points for each element and parameter analysed.
	Size of study	3,450 subjects for which complete Mini-Mental State Examination (MMSE) was available and 3,430 subjects for whom covariates were also collected.
Exposure and setting	Exposure pathway	Drinking water
	Source of chemical/ contamination	Water supply
	Exposure concentrations (if applicable)	For each drinking water area, a weighted mean of the measures of each component of drinking water available from the water supplies used in the area was calculated; the weighting took into account the length of the period of use of each water supply over the previous 10 years and the hourly flow or relative contribution of each water supply. Silica concentrations (mg/L): • Minimum: 4.2 • 1st quartile: 10.4 • Median: 11.2 • 3rd quartile: 12.4 • Maximum: 22.4
	Comparison group(s)	Not applicable (results divided in quartiles)
Study methods	Water quality measurement used	Samples divided into 71 drinking water areas for which measurements were available.
	Water sampling methods (monitoring, surrogates)	Information provided by sanitary administration. All results of chemical analyses of drinking water carried out since 1991. Silica was measured by colorimetry.
Results (for each outcome)	Definition of outcome	

Publication Reference: Jacqmin-Gadda H., Commenges D., Letenneur L. and Dartigues J. F. (1996). Silica and aluminum in drinking water and cognitive impairment in the elderly. Epidemiology 7(3): 281-285.		
	How outcome was assessed	• Cognitive status. For three categories (low, medium, high) defined by the first and last quartiles of the distribution of the concentrations of silica, the crude prevalence of cognitive impairment was 24.0% (N = 775), 21.8% (N = 1,828), and 28.3% (N = 847), respectively. The prevalence did not decrease when the silica concentration increased, but rather, it exhibited a U-shape. • High silica was not associated with hard or acid water. Negative correlation between Al and Si levels is very low in the data. • When the level of silica and the pH were both low, subjects exposed to an aluminium concentration above 3.5 µg/L appeared more likely to have cognitive impairment when compared with subjects not exposed to aluminium (OR = 3.94), whereas, when the level of silica and the pH were both high, subjects exposed to aluminium appeared less likely to be cognitively impaired than subjects not exposed (Odds Ratio, OR = 3.94 X 0.58 X 0.31 = 0.71).
	Method of measurement	Cognitive status measured by the Mini-Mental State Examination (MMSE) which evaluates orientation to time and place, simple arithmetic, registration and recall of three objects, simple language tasks, and visuo-constructional abilities. The score ranges from 0 to 30; cognitive impairment was defined as a score less than 24.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	See above
Statistics (if any)	Statistical method used	• A mixed effects logistic regression to take into account the grouping of the subjects in parishes and to adjust for the major individual risk factors: age, sex, educational level, and principal lifetime occupation. This regression model accounts for the residual correlation of the observations in the parishes that could be due to some characteristics of the parishes not included in the model. • Calcium was entered as a binary variable, with 75 mg per litre (the median) as the cutpoint. Included aluminium, pH, and silica as binary variables. Analyses presented based on three cutpoints for the pH and the concentrations of aluminium and silica (first quartile, median, or third quartile) because they led to different results. • The category "high aluminium, high silica, and high pH" had a lower risk of cognitive impairment than the class "low aluminium, high silica, and high pH" (OR = 0.75), and this result relies on a larger number of regions. • Finding indicates a paradoxical protective effect of aluminum for some levels of silica and pH. When pH was low and the concentration of silica was high, the OR of the effect of aluminium was close to one (OR = 0.74/ 0.64 = 1.16).
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	See above

Publication Reference: Jacqmin-Gadda H., Commenges D., Letenneur L. and Dartigues J. F. (1996). Silica and aluminum in drinking water and cognitive impairment in the elderly. Epidemiology 7(3): 281-285.		
Author's conclusions	Interpretation of results	• Results support the hypothesis of a protective effect of silica against the aluminium from drinking water, as opposed to protection against all sources of dietary aluminium. Indeed, a high concentration of aluminium in drinking water appeared to increase the risk of cognitive impairment only when the silica level was low. This finding could be explained by a change in the bioavailability of aluminium from drinking water when silica is present. It is difficult, however, to explain why aluminium may be protective when pH and silica levels are both high.
	Assessment of uncertainty (if any)	• As hypothesised, authors found a greater OR for high aluminium, low silica, and low pH, but this category included only four regions, and thus the estimate has a large confidence interval. • If dietary aluminium intake is highly variable, findings might be biased because authors did not adjust for total daily Al intake, which is difficult to measure. • Concentrations of silica in the sample was high. • Exposure was measured only at the community level.
Reviewer comments	Results included/excluded in review (if applicable)	• This study indicated no significant association between silicon concentration and cognitive impairment, but suggested a protective effect of silica against aluminium from drinking water (a high concentration of aluminium in drinking water appeared to increase the risk of cognitive impairment only when the silica level was low). • Study may inform on hazard identification in humans, therefore was subjected to further review and risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

Jugdaohsingh et al. 2008

Publication Reference: Jugdaohsingh R., Calomme M. R., Robinson K., Nielsen F., Anderson S. H., D'Haese P., Geusens P., Loveridge N., Thompson R. P. and Powell J. J. (2008). Increased longitudinal growth in rats on a silicon-depleted diet. Bone 43(3): 596-606.		
General Information	Date of data extraction	27/05/2023
	Authors	Jugdaohsingh R, Calomme MR, Robinson K, Nielsen F, Anderson SHC, D'Haese P, Geusens P, Loveridge N, Thompson RPH, Powell JJ
	Publication date	2008
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	UK, Belgium, USA, Netherlands

Publication Reference: Jugdaohsingh R., Calomme M. R., Robinson K., Nielsen F., Anderson S. H., D'Haese P., Geusens P., Loveridge N., Thompson R. P. and Powell J. J. (2008). Increased longitudinal growth in rats on a silicon-depleted diet. Bone 43(3): 596-606.		
	Source of funding	Supported by the Institute for the Promotion of Innovation by Science and Technology in Flanders (IWT, Belgium, project 000290) and the Frances Augustus Newman Foundation (fellowship for RJ). The Wellcome Trust funded the ICPOES facility and the charitable foundation of The Institute and Guild of Brewing provides running costs for the Si research program (RJ, JJP and RPHT).
	Possible conflicts of interest	No conflict of interest statement was included in the paper.
Study characteristics	Aim/objectives of study	To determine the role of Si in growth and development, and in particular skeletal development, in the rat using a specifically formulated low Si-containing feed and a low Si-containing drinking water with and without Si supplementation.
	Study type/design	Experimental animal study
	Study duration	26 weeks
	Type of water source (if applicable)	Ultra-high purity water
Population characteristics	Population/s studied	Weanling (21-d old) female Sprague Dawley rats; 5 rats/cage.
	Selection criteria for population (if applicable)	
	Subgroups reported	3 dietary groups: • Group 1 (Si-deprived): n=20 rats fed *ad libitum* a formulated non-pelleted low-Si rodent feed (containing 3.2 mg/kg) and ultra high purity (UHP) water with low Si content (15.2 µg/L) *ad libitum*. • Group 2 (Si-supplemented): n=10 rats similarly treated to Group 1 but the drinking water was supplemented with silicon at 53.2 mg/L in the form of readily absorbable orthosilicic acid. • Group 3 (reference group): n=10 maintained on standard rodent stock feed (322 mg/kg) and tap water (5.04 mg/L) *ad libitum*.
	Size of study	N=40 rats
Exposure and setting	Exposure pathway	Food and drinking water
	Source of chemical/ contamination	Orthosilicic acid supplementation of drinking water, Si supplementation of feed. Concentrated basic sodium silicate (Aldrich Chemical Co., Poole, UK) was diluted in 2.5 L UHP water, followed by pH neutralisation to 7.2 with 5 mol/L hydrochloric acid (volumetric standard; Aldrich Chemical Co.). The solution was allowed to stand at room temperature for at least 24 h prior to use.
	Exposure concentrations (if applicable)	• 3.19 mg Si/kg feed in low silicon diet. • 322.4 mg Si/kg feed in standard rodent diet

Publication Reference: Jugdaohsingh R., Calomme M. R., Robinson K., Nielsen F., Anderson S. H., D'Haese P., Geusens P., Loveridge N., Thompson R. P. and Powell J. J. (2008). Increased longitudinal growth in rats on a silicon-depleted diet. Bone 43(3): 596-606.		
	Comparison group(s)	A group of rats on a standard rodent stock feed and drinking water served as reference for normal anthropogenic measures. The standard rodent stock feed was higher in Si content than the formulated low-Si feed. Still, however, due to other nutritional differences, the two diets were not compared in this study with regards to the effect of silicon.
Study methods	Water quality measurement used	Total elemental analysis was carried out by inductively coupled plasma optical emission spectrometry.
	Water sampling methods (monitoring, surrogates)	Feeds (0.1–0.3 g) were digested in 10 mL of a 1 + 1 mixture of UHP nitric acid (65% w/v; Fluka; Aldrich-Sigma Chemical Co.) and UHP water in acid-cleaned 100 mL TFM vessels in an Ethos Plus Microwave Labsystem. Microwave conditions were: 10 min ramp to 180 °C and maintained at 180 °C for 15 min. Blanks (acid mixture without sample) were also prepared and 'digested' in parallel. The cooled digested samples and blanks were transferred into cleaned, pre-weighed polypropylene 60 mL bottles (WVR International Ltd) and diluted with 10 mL UHP water.
Results (for each outcome)	Definition of outcome	• Rat weights and lengths measured weekly. Blood sample collected monthly from 6-hour fasted rats for longitudinal analysis of bone markers. Urine sample collected towards end of study (week 25) from fasted rats for assessment of urinary bone resorption markers and urinary Si excretion. Serum at sacrifice analysed for bone markers and Si concentration. Organ weights determined. Tibia subjected to histomorphometric analysis. Dissected bones were analysed for bone mineral density, Si and other bone-associated mineral content, hydroxyproline concentration, mechanical strength and histomorphometry.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	See above subgroup information.
Statistics (if any)	Statistical method used	• Differences between the Si-deprived and Si-supplemented groups were analysed by unpaired two-tailed Student's t-test with significance taken as $P<0.05$. Results are reported without adjustment for multiple comparisons, but authors have also reported where results would remain significant with a simple and non-conservative Bonferroni correction (i.e. P/n) where results are part of a larger group (e.g. bone markers). Repeat measurements (RM)-analysis of variance (ANOVA) was used for assessment of weekly body weights and lengths and, monthly serum CTX and osteocalcin measurements over the study period. These were conducted in SPSS for Windows
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable

Publication Reference: Jugdaohsingh R., Calomme M. R., Robinson K., Nielsen F., Anderson S. H., D'Haese P., Geusens P., Loveridge N., Thompson R. P. and Powell J. J. (2008). Increased longitudinal growth in rats on a silicon-depleted diet. Bone 43(3): 596-606.		
Author's conclusions	Interpretation of results	• The estimated mean ± SD daily intake of Si at 17 and 25 weeks (i.e. from feed plus water) was 0.17 ±0.04 mg/kg body weight for the rats in the Si-deprived group and 4.08 ±0.74 mg/kg body weight in the supplemented group. Dietary silicon intake in the Si-supplemented animals was thus 24 times that of the Si-deprived group. In the standard rodent stock feed-fed reference group, estimated daily Si intake was 18.51 ± 0.65 mg/kg body weight. Due to other nutritional differences, the two diets were not compared in this study with regards to the effect of silicon on the rats. Rats on the standard rodent stock feed served only as a reference for normal anthropogenic measures. • Selective Si deprivation led to a minor drop in serum Si concentrations but a marked fall in urinary Si output. The current paradigm is that orthosilicic acid [$Si(OH)_4$] – a small soluble, labile (i.e. weak or negligible interactions with proteins and other biomolecules) and neutral species – follows the water pool and thus, following absorption, is excreted in line with renal filtration without either active excretion or retention. In the reference group of standard rodent stock feed-fed animals the ratio of urinary Si (creatinine corrected): serum Si concentrations was 11 ± 6, and similar to that of the Si-supplemented group of 20 ± 14. However, in the Si-deprived animals the ratio was 3 ± 3. This suggests that, in states of Si deprivation, urinary Si conservation, perhaps through renal reabsorption, can occur. • Si supplementation of drinking water did not change bone Si concentrations. The lack of incorporation into bone was not a failure of absorption but, rather, one of utilisation. This may suggest that some co-factor, probably nutritional, is required for maximal Si uptake into bone and that this co-factor was absent for animals on the formulated low-Si feed. • Si supplementation had no effect on bone Si concentrations or on multiple markers of bone quality when using the specially formulated low-Si feed, but authors did observe effects on certain other outcomes. There were clear differences in (a) the phosphorus content of bone (b) the length of the animals from week 18 onwards, and (c) the length of the bones at necropsy, with an apparent reduction in growth plate thickness and an increase in chondrocyte density. These data may indicate that while circulating Si can influence chondrocyte function directly (c.f. correlations between bone lengths and serum Si), effects on osteoblast function and/or bone quality may require the incorporation of Si into bone.

Publication Reference: Jugdaohsingh R., Calomme M. R., Robinson K., Nielsen F., Anderson S. H., D'Haese P., Geusens P., Loveridge N., Thompson R. P. and Powell J. J. (2008). Increased longitudinal growth in rats on a silicon-depleted diet. Bone 43(3): 596-606.		
	Assessment of uncertainty (if any)	• As with many studies since the 1970s, authors were unable to reproduce the profound Si deficiency state reported in rats and chickens previously. The authors presume that either the dietary Si levels were still too high in the Si-deprived formulated diet, or that these older studies were observing some co-deficiency with their diets, or that the diet in the current study produced some co-deficiency that did not allow Si incorporation into bone. It is also possible that the animals in this study were pre-loaded with Si perinatally, prior to transfer to the low-Si diet at three weeks of age.
Reviewer comments	Results included/excluded in review (if applicable)	• Although only a limited number of specific endpoints were investigated in this study, it does provide an indication that a total dose of Si (from feed and water) of 4.08 ±0.74 mg/kg body weight in the supplemented group and perhaps 18.51 ± 0.65 mg/kg in the referent group did not result in adverse effects after 26 weeks of exposure. There is uncertainty regarding the latter exposure since due to other nutritional differences, the two diets were not compared in this study with regards to the effect of silicon on the rats. Rats on the standard rodent stock feed served only as a reference for normal anthropogenic measures. Nevertheless, no mention of adverse effects in the control group was made in the paper. • As the study provides some information on dose response, it was subjected to further review and risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

Jugdaohsingh et al. 2015a

Publication Reference: Jugdaohsingh R., Kessler K., Messner B., Stoiber M., Pedro L. D., Schima H., Laufer G., Powell J. J. and Bernhard D. (2015a). Dietary Silicon Deficiency Does Not Exacerbate Diet-Induced Fatty Lesions in Female ApoE Knockout Mice. J Nutr 145(7): 1498-1506.		
General Information	Date of data extraction	27/05/2023
	Authors	Jugdaohsingh R, Kessler K, Messner B, Stoiber M, Pedro LD, Schima H, Laufer G, Powell JJ, Bernhard D
	Publication date	2015
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	UK and Austria
	Source of funding	R Jugdaohsingh received funding (salary) from the Grants Committee of the Institute of Brewing and Distilling (United Kingdom) to carry out the work. The silicon supplement, monomethylsilanetriol, was provided by LLR-G5 Ltd. (Castlebar, Ireland). All remaining costs were met through core institutional funds: Medical Research Council (grant number MC_US_A090_0008/Unit Program number U1059).

Publication Reference: Jugdaohsingh R., Kessler K., Messner B., Stoiber M., Pedro L. D., Schima H., Laufer G., Powell J. J. and Bernhard D. (2015a). Dietary Silicon Deficiency Does Not Exacerbate Diet-Induced Fatty Lesions in Female ApoE Knockout Mice. J Nutr 145(7): 1498-1506.		
	Possible conflicts of interest	R Jugdaohsingh, K Kessler, B Messner, M Stoiber, LD Pedro, H Schima, G Laufer, and D Bernhard, no conflicts of interest. JJ Powell has consulted to the silicon supplement industry including LLR-G5 Ltd. (Castlebar, Ireland). The research was designed, executed, analysed, and communicated only by the authors.
Study characteristics	Aim/objectives of study	To investigate the effect of dietary silicon on 1) serum and aorta silicon concentrations, 2) the development of aortic lesions and serum lipid concentrations, and 3) the structural and biomechanic properties of the aorta in mice lacking the *apoE* gene (and therefore susceptible to atherosclerosis).
	Study type/design	Experimental animal study
	Study duration	15-19 weeks
	Type of water source (if applicable)	Sterile, low-silicon containing deionised drinking water from Sigma-Aldrich Co.
Population characteristics	Population/s studied	Female C57BL/6J-ApoE/J mice, i.e. female apoE knockout mice. Random allocation to study groups.
	Selection criteria for population (if applicable)	
	Subgroups reported	Three groups (n=9-15 mice/group): 1) Silicon deprived (-Si): Received a specifically formulated high-fat diet (21% weight anhydrous milk fat and 1.5% weight cholesterol) with low silicon (<3 µg silicon/g) as well as low-silicon drinking water (0.04 µg silicon/mL) *ad libitum*. 2) Silicon-replete (+Si) in feed (+Si-feed) group: received the same high-fat feed but the feed was replete in silicon at 100-µg silicon/g feed (i.e. 100 mg/kg feed), as sodium metasilicate. This is still relatively low in silicon compared to normal murine laboratory maintenance feed (R/M-H), which was found to contain 669 ± 60 µg silicon/g feed (669 mg/kg feed). However, sodium metasilicate is readily bioavailable unlike much of the silicon naturally present in laboratory rodent diets. Drinking water consisted of the low-silicon water. 3) Silicon-replete in drinking water (+Si-water) group: received the same high-fat, low-silicon feed as group 1, but their drinking water was replete in silicon at 115 µg silicon/mL (i.e. 115 mg/L) in the form of monomethylsilanetriol [$CH_3Si(OH)_3$]. It is metabolised *in vivo* to orthosilicic acid, $Si(OH)_4$, and is a convenient form of soluble silicon for dosing unlike orthosilicic acid because it does not polymerise at the concentration used here.

Publication Reference: Jugdaohsingh R., Kessler K., Messner B., Stoiber M., Pedro L. D., Schima H., Laufer G., Powell J. J. and Bernhard D. (2015a). Dietary Silicon Deficiency Does Not Exacerbate Diet-Induced Fatty Lesions in Female ApoE Knockout Mice. J Nutr 145(7): 1498-1506.		
	Size of study	Two studies: • Study 1: Investigated effect of the dietary Si on the formation of fatty streak lesions (early atherosclerotic plaques). The -Si group consisted of 9 mice, whereas the +Si groups consisted of 10 mice. Mice were 4–6 weeks old at the start of the intervention. Dietary intervention lasted for 15 week. One mouse in the -Si group was killed at 11 week to check for the development of fatty streak lesions. This was found to be low, so the remaining mice were maintained on their respective diets for an additional 4 weeks. One mouse in the -Si group died during the study (week 8). The cause of death was unclear, but it is unlikely to be related to the treatment received. This left only 7 mice in the -Si group at the end of the study. • Study 2: investigated the effect of the dietary silicon on total serum lipids and on the structural and biomechanic properties of the aorta (tensile strength, elasticity, collagen and elastin content, and elastin structure and morphology). Groups consisted of 15 mice in the -Si group and 10 mice in the +Si groups. Mice were 16–17 weeks old at the start of the intervention and were maintained on their respective diets for up to 19 weeks.
Exposure and setting	Exposure pathway	Food and drinking water
	Source of chemical/ contamination	Monomethylsilanetriol added to drinking water.
	Exposure concentrations (if applicable)	Si intakes (mg/kg bw) (from supplementary material). Study 1: • -Si: 1.1 ± 0.36 • +Si feed: 57.4 ± 20.9 • +Si water: 20.7 ± 7.1 Study 2: • -Si: 0.36 ± 0.22 • +Si feed: 24.0 ± 9.7 • +Si water: 14.6 ± 6.4
	Comparison group(s)	In both studies, 5 mice were collected before separation into the 3 dietary silicon groups. The ‘‘baseline’’ samples from these mice indicate the magnitude of the changes (e.g. in plasma lipid concentrations) caused by the dietary interventions. However, because of the small numbers, these baseline samples were not compared statistically with the treatment groups.
Study methods	Water quality measurement used	*“Feed and drinking water samples were also analyzed for total silicon with appropriate standards.”* Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES)
	Water sampling methods (monitoring, surrogates)	Feed and water intakes measured at 9 and 11 weeks in Study 1 and at 1 and 15 weeks in Study 2.
Results (for each outcome)	Definition of outcome	

Publication Reference: Jugdaohsingh R., Kessler K., Messner B., Stoiber M., Pedro L. D., Schima H., Laufer G., Powell J. J. and Bernhard D. (2015a). Dietary Silicon Deficiency Does Not Exacerbate Diet-Induced Fatty Lesions in Female ApoE Knockout Mice. J Nutr 145(7): 1498-1506.		
	How outcome was assessed	• Outward appearance of mice checked every 2nd day, weighed weekly, blood sample taken monthly, after sacrifice organ aorta and heart examined in detail. • The serum silicon concentration in the -Si group was significantly lower than in the +Si-feed (by up to 78%; P <0.003) and the +Si-water (by up to 84%; P < 0.006) groups. The aorta silicon concentration was also lower in the -Si group than in the +Si-feed group (by 65%; P = 0.025), but not compared with the +Si-water group. There were no differences in serum and aorta silicon concentrations between the silicon-replete groups. Body weights, tissue wet weights at necropsy, and structural, biomechanic, and morphologic properties of the aorta were not affected by dietary silicon; nor were the development of fatty lesions and serum lipid concentrations.
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	See above
Statistics (if any)	Statistical method used	• All 3 dietary silicon groups were compared with each other. One-factor ANOVA was used to compare means for feed intake, water intake, serum lipid concentrations, deposition of fatty lesions, aortic circumference, aortic collagen concentration, and aortic elastin concentration. Significant difference was taken as P < 0.05. • The independent samples Kruskal-Wallis test with pairwise comparison was used to assess the means for silicon intake, total serum silicon concentration, and aorta silicon concentration because these data were not normally distributed. Significance was taken as P < 0.05. • Repeated-measures ANOVA was used to assess body weight over the study period and biomechanic measures (i.e. maximum tear force, elasticity, and circumference) along the 7 aortic positions, with significant group differences taken as P <0.05. Bonferroni post hoc analysis was used to determine the significant differences in maximum tear force.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Findings suggest dietary silicon has no effect on atherosclerosis development and vascular health in the apoE mouse model of diet-induced atherosclerosis, contrary to the reported findings in the cholesterol-fed rabbit model.

Publication Reference: Jugdaohsingh R., Kessler K., Messner B., Stoiber M., Pedro L. D., Schima H., Laufer G., Powell J. J. and Bernhard D. (2015a). Dietary Silicon Deficiency Does Not Exacerbate Diet-Induced Fatty Lesions in Female ApoE Knockout Mice. J Nutr 145(7): 1498-1506.		
	Assessment of uncertainty (if any)	• It is possible that, although serum silicon concentrations were lower in the -Si group, than in the +Si groups, the mice may not have been deficient in silicon. Indeed, the lack of significant difference in aortic silicon concentrations between the -Si and +Si-water groups would imply this to be the case, and this could explain the lack of difference in structural and biomechanical properties of the aortas between the dietary silicon groups. • Further work, in a dietary-based rather than ''genetically programmed'' model of atherosclerosis, is now needed to corroborate these findings.
Reviewer comments	Results included/excluded in review (if applicable)	• Although only a limited number of specific endpoints were investigated in this study, it does provide an indication that a total dose of Si (from feed and water) of up to 57.4 mg/kg body weight did not result in adverse effects after 15-19 weeks of exposure. • As the study provides some information on dose response, it was subjected to risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

Junnila 2011

Publication Reference: Junnila S. K. (2011). Nanocolloidal amorphous silica in drinking water as an autoimmunity trigger in Finland. Med Hypotheses 77(5): 815-817.		
General Information	Date of data extraction	28/05/2023
	Authors	Junnila SK
	Publication date	2011
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	Finland
	Source of funding	No grants.
	Possible conflicts of interest	None declared.
Study characteristics	Aim/objectives of study	Mini-review providing observations to support the hypothesis that amorphous silica/humus/iodine nanocolloid particles in tap water are internalised by thyrocytes via the sodium iodide symporter (NIS) and subsequently denature various intracellular protein, thereby affecting immunoreactivity of proteins which trigger the autoimmunity process.
	Study type/design	Mini-review
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
	Population/s studied	Not applicable

Publication Reference: Junnila S. K. (2011). Nanocolloidal amorphous silica in drinking water as an autoimmunity trigger in Finland. Med Hypotheses 77(5): 815-817.		
Population characteristics	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/ contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• Crystalline silica dissolves in water; the solubility is about 6 ppm SiO_2. The dissolved silica is named (ortho)silicic acid ($Si(OH)_4$). • Amorphous silica (ASi) is more soluble in water than crystalline silica (about 100 ppm SiO_2), this is true in particle size down to nm-scale. ASi is hydrated, that is, it contains water as OH groups, which are reactive. It has been known for more than 150 years that ASi is a component of soil and natural waters. Almost all soils contain about 2–3% Asi. • Natural waters contain both quartz and ASi in the form of nanosized colloidal particles. These particles are solubilised so that in particle size over approximately 5 nm Asi is more soluble, but in particle size under approximately 5 nm quartz is more soluble. • Previously, it was observed that high iodine concentrations in the raw (ground) water of a water treatment plant wells in Finland is associated with a high prevalence of autoimmune hypothyreosis in consumers. • Water sources in the Finland municipalities with a high prevalence of autoimmune hypothyreosis are at least at times synclinal (the water flows from the flood lake to the aquifer). This kind of flood lake is a suitable environment for the synthesis of ternary system amorphous silica/humus/iodine nanocolloid (Asi/Hu/I) particles. • The authors present a proposed hypothesis that Asi/Hu/I nanocolloid particles in tap water are internalised by thyrocytes via the sodium iodide symporter (NIS), indicating receptor-mediated endocytosis. Receptor-mediated endocytosis is quick and efficient so that enough amorphous silica nanoparticles are internalised inside thyrocytes to denature various intracellular proteins (e.g. thyroglobulin), thereby affecting the immunoreactivity of proteins, which triggers the autoimmunity process.
	How outcome was assessed	
	Method of measurement	

Publication Reference: Junnila S. K. (2011). Nanocolloidal amorphous silica in drinking water as an autoimmunity trigger in Finland. Med Hypotheses 77(5): 815-817.		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• The authors present a number of observations from the literature that support their hypothesis.
	Assessment of uncertainty (if any)	• The authors suggest an interscience study of nanocolloidal ASi and its effects on people's health in Finland should be performed.
Reviewer comments	Results included/excluded in review (if applicable)	• This mini-review presents a potential hypothesis for the role of natural amorphous silica nanoparticles in the development of autoimmune disease (specifically hypothyreosis). • However, this is very much just a hypothesis with suggestions for additional research to investigate the potential. Therefore this paper is not deemed a critical study and has been excluded from further assessment and was not subjected to risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

Lewinson et al. 1994

Publication Reference: Lewinson J., Mayr W. and Wagner H. (1994). Characterization and toxicological behavior of synthetic amorphous hydrophobic silica. Regul Toxicol Pharmacol 20(1 Pt 1): 37-57.		
General Information	Date of data extraction	28/05/2023
	Authors	Lewinson J, Mayr W, Wagner H
	Publication date	1994
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	USA and Germany
	Source of funding	Not stated
	Possible conflicts of interest	No conflict of interest statement in paper. It is noted the authors are from Degussa, the manufacturers of the tested material.
Study characteristics	Aim/objectives of study	To report on test results in experimental animals for modified hydrophobic silicas (97-99% silicon dioxide).
	Study type/design	Experimental animal studies

Publication Reference: Lewinson J., Mayr W. and Wagner H. (1994). Characterization and toxicological behavior of synthetic amorphous hydrophobic silica. Regul Toxicol Pharmacol 20(1 Pt 1): 37-57.		
	Study duration	1) Acute study: Single dose, 14-day observation 2) Subacute study: Fumed Hydrophobic Silica (FHS) 5 weeks in low- and mid-dose groups, 8 weeks in high-dose group. 3) Chronic oral toxicity: 6 months with a 3-week recovery period. 4) Carcinogenicity study: 24 months 5) Reproductive toxicity: Exposure pre-mating, during mating (week 8-17) with pre-exposed males; total treatment period = 6 months with a 3-week recovery period.
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	1) Acute study: Sprague-Dawley rats (100-105g) 2) Subacute study: Wistar rats 3) Chronic oral toxicity: Wistar rats (117g for males, 131g for females) 4) Carcinogenicity study: Wistar rats (70 g) 5) Reproductive toxicity: Female Wistar rats (120 ± 4g)
	Selection criteria for population (if applicable)	
	Subgroups reported	1) Acute study: 10/sex/dose (FHS), 5/sex/dose (precipitated hydrophobic silica, PHS) 2) Subacute study: 10/sex/dose (FHS) 3) Chronic oral toxicity: 20/sex/dose 4) Carcinogenicity study: 20/sex/dose 5) Reproductive toxicity: 10/dose
	Size of study	1) Acute study: n=60 FHS, n=40 PHS 2) Subacute study: n=80 FHS 3) Chronic oral toxicity: n=80 FHS 4) Carcinogenicity study: n=80 FHS 5) Reproductive toxicity: n=20 FHS
Exposure and setting	Exposure pathway	1) Acute study: Gavage 2) Subacute study: Diet 3) Chronic oral toxicity: Diet 4) Carcinogenicity study: Diet 5) Reproductive toxicity: Diet
	Source of chemical/ contamination	Sipernat D17 (PHS) and Aerosil R972 (FHS) manufactured by Degussa.
	Exposure concentrations (if applicable)	1) Acute study: 2500 or 5000 mg/kg FHS in peanut oil; 5040, 6350 or 7900 mg/kg PHS in olive oil 2) Subacute study: 0, 500, 1000, or 2000 (elevated to 4000 after 14 days, to 8000 after another 14 days, and finally to 16,000) mg/kg FHS 3) Chronic oral toxicity: 0 or 500 mg/kg FHS for 6 months with an additional 3-week recovery period. 4) Carcinogenicity study: 0 or 100 mg/kg FHS 5) Reproductive toxicity: 0 or 500 mg/kg FHS
	Comparison group(s)	Control included in each study

Publication Reference: Lewinson J., Mayr W. and Wagner H. (1994). Characterization and toxicological behavior of synthetic amorphous hydrophobic silica. Regul Toxicol Pharmacol 20(1 Pt 1): 37-57.		
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	1) Acute study: No deaths and no signs of toxicity. LD50s >5,000 mg/kg for FHS and >7,900 mg/kg for PHS (highest doses tested). 2) Subacute study: a. Treatment-related effects only observed in stepwise increased high dose of 16,000 mg/kg; these consisted of shyness, dirty fur, reduced activity, cachexia, and haemorrhage in mucus membranes of eyes and nose with death of 2 males and 2 females on days 9 and 13 after administration of 16,000 mg/kg. After 8,000 mg/kg only a slight decrease in body weight was observed. b. Severe atrophy in epithelium of liver from rats consuming highest dose (2,000 – 16,000 mg/kg). These changes were sporadically seen to a lesser degree in mid-dose (1000 mg/kg). NOEL = 500 mg/kg. 3) Chronic oral toxicity: a. No clinical signs or behavioural changes. One male (lung infection) in treated group and one male and one female (enteritis followed by cachexia) in control groups died. b. The histopathological examinations revealed an increased lipid content in the fasciculata and the zone fasciculata of the adrenal glands. This effect appeared to resolve during the 3-week treatment-free period. This slight progressive transformation in the adrenals was regarded as reversible and was attributed to chronic stress. c. NOAEL = 500 mg/kg/d 4) Carcinogenicity study: a. No treatment-related carcinogenic effects observed. NOAEL = 100 mg/kg/d. 5) Reproductive toxicity: No treatment related effects, NOAEL of 500 mg/kg/d.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	See above
Statistics (if any)	Statistical method used	Not stated
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable

Publication Reference: Lewinson J., Mayr W. and Wagner H. (1994). Characterization and toxicological behavior of synthetic amorphous hydrophobic silica. Regul Toxicol Pharmacol 20(1 Pt 1): 37-57.		
Author's conclusions	Interpretation of results	• Biological studies of silica, silicones, and methylpolysilicones available in the public literature suggest that they are virtually nontoxic at use levels currently used in food and food-contact materials. Their toxicological properties are believed to be moderated greatly by their non-absorbability. Likewise, the large effective molecular weights and large particle sizes of hydrophobic silicas suggest that their toxicological properties should not be significantly different from other silica-based products. In fact, they have essentially the same general structure as silicas: they are insoluble in water, chemically inert, and highly unlikely to be significantly absorbed from the gastrointestinal system. • The studies reported in this article confirm the absence of significant acute, subchronic, chronic, and reproductive toxicity of hydrophobic silicas by external, inhalation, and oral routes of exposure (note the data extraction here focused on oral studies).
	Assessment of uncertainty (if any)	Not undertaken
Reviewer comments	Results included/excluded in review (if applicable)	• Note the results presented in this study are for methylated (i.e. hydrophobic) amorphous nanosilicas (7-22 nm in size) which may not be entirely comparable to silicas originating from silicon brasses. • Nevertheless, the study provides results for a standard toxicological package of studies conducted with FHS, which support the absence of toxicity observed in oral acute, subacute, chronic, and carcinogenicity studies. Lowest NOAEL = 100 mg/kg/d from 24-month carcinogenicity study. • As the paper provides dose response information, it was subjected to risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

Liang et al. 2018

Publication Reference: *Liang, C.L, Xiang, Q., Cui, W.M., Fang, Jin., Sun, N.N., Zhang, X.P., Li, Y.N., Yang, H., Yu, Z., Jia X.D. (2018). Subchronic Oral Toxicity of Silica Nanoparticles and Silica Microparticles in Rats. Biomed Environ Sci, 2018; 31(3): 197-207*		
General Information	Date of data extraction	30/05/2023
	Authors	Liang CL, Xiang Q, Cui WM, Fang Jin, Sun NN, Zhang XP, Li YN, Yang H, Yu Z, Jia XD
	Publication date	2018
	Publication type	Peer-reviewed journal article
	Peer reviewed?	No
	Country of origin	China
	Source of funding	Not stated

Publication Reference: *Liang, C.L, Xiang, Q., Cui, W.M., Fang, Jin., Sun, N.N., Zhang, X.P., Li, Y.N., Yang, H., Yu, Z., Jia X.D. (2018). Subchronic Oral Toxicity of Silica Nanoparticles and Silica Microparticles in Rats. Biomed Environ Sci, 2018; 31(3): 197-207*		
	Possible conflicts of interest	No conflict of interest statement in paper. It is noted the authors are from the Key Laboratory of Food Safety Assessment of Ministry of Health (China National Center for Food Safety Risk Assessment) or Sichuan Province Medical Science Academy & Sichuan Provincial People's Hospital.
Study characteristics	Aim/objectives of study	To investigate the subchronic oral toxicity of silica nanoparticles (NPs) and silica microparticles (MPs) in rats and to compare the difference in toxicity between two particle sizes.
	Study type/design	Experimental animal studies
	Study duration	90-day subchronic oral toxicity study
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	10/sex/dose (3 exposure groups and 1 control group)
	Size of study	140 healthy weanling Sprague-Dawley rats
Exposure and setting	Exposure pathway	Gavage
	Source of chemical/ contamination	Hydrophilic precipitated silica microparticles were purchased from Aladdin Industrial Inc. (Shanghai, China) without surface modification and stored at room temperature
	Exposure concentrations (if applicable)	0, 166.7, 500, and 1,500 mg/kg bw/d
	Comparison group(s)	Control included in each study
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	There were no mortality or treatment related adverse clinical reactions and no remarkable gross pathological alterations found during the study. Differences identified in body weight and food consumption were of no clinical significance (no dose response and did not occur continuously). The clinical biochemical analysis indicated some isolated statistically significant changes in treatment groups.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	20 animals in the control group and 60 animals in the three exposure groups (20 animals each) for silica microparticles (and a further 60 animals for the three nanoparticles exposure groups).
Statistics (if any)	Statistical method used	• Organ data, body weights, food consumption, biochemical and serum data: one-way analysis of variance (ANOVA) • Homogeneity of variances: Levene's test • Comparisons between multiple groups: Bonferroni's post hoc test or Dunnett's T3 post hoc
	Details on statistical analysis	

Publication Reference: *Liang, C.L, Xiang, Q., Cui, W.M., Fang, Jin., Sun, N.N., Zhang, X.P., Li, Y.N., Yang, H., Yu, Z., Jia X.D. (2018). Subchronic Oral Toxicity of Silica Nanoparticles and Silica Microparticles in Rats. Biomed Environ Sci, 2018; 31(3): 197-207*		
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• There were no dose-related changes upon administration of silica microparticles in any exposure group compared with the control group. There was no absorption of silica from the gastrointestinal tract into the blood, liver, kidneys, and testis. • Note that there was no difference in toxicity or silica distribution between silica nanoparticles and silica microparticles.
	Assessment of uncertainty (if any)	Not undertaken
Reviewer comments	Results included/excluded in review (if applicable)	• The subchronic NOAEL = 1,500 mg/kg/d, the highest dose tested. • As the paper provides dose response information, it was subjected to risk of bias assessment. • Note the results for the Silica nanoparticles are not discussed above. Nonetheless, the findings would remain the same (no treatment related effects and a NOAEL of 1,500 mg/kg/d).

Markovic and Arambasic 1971

Publication Reference: Markovic B and Arambasic MD (1971). Experimental chronic interstitial nephritis compared with endemic human nephropathy. Journal of Pathology. 103: 35-40		
General Information	Date of data extraction	27/06/2023
	Authors	Markovic B and Arambasic MD
	Publication date	1971
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Yugoslavia
	Source of funding	Funding sources not specified (authors are from Institute for Health Protection)
	Possible conflicts of interest	No conflict of interest statement included in the paper.
Study characteristics	Aim/objectives of study	To report the experimental induction of chronic interstitial nephritis by a quartz suspension and compare the induced renal lesions with the histopathological changes found in endemic nephropathy in humans.
	Study type/design	Experimental animal study
	Study duration	Up to 6 months

Publication Reference: Markovic B and Arambasic MD (1971). Experimental chronic interstitial nephritis compared with endemic human nephropathy. Journal of Pathology. 103: 35-40		
	Type of water source (if applicable)	'Clean' drinking water from Beograd waterworks, suitable for human consumption. Concentration of 50 and 250 mg/L of pure quartz (SiO_2) suspension was used from the mount of Bukulja provided by a geologist from the Institute of Nuclear Raw Material in Beograd. It was ground in a mortar and the size of particles measured under a microscope.
Population characteristics	Population/s studied	Guinea pigs >6 months of age (>500g).
	Selection criteria for population (if applicable)	
	Subgroups reported	• Treated groups: 50 or 250 mg SiO_2/L (20 animals/group) • Control group: 20 guinea pigs fed with oats for the first 5 days in the week, then supplemented with carrots for the last 2 days each week. They were given 'clean' water for the first 5 days, then deprived of water the last 2 days each week.
	Size of study	60 animals
Exposure and setting	Exposure pathway	Oral (drinking water)
	Source of chemical/ contamination	Pure quartz (SiO_2) suspension was used from the mount of Bukulja provided by a geologist from the Institute of Nuclear Raw Material in Beograd. It was ground in a mortar and the size of particles measured under a microscope. Quartz (finely ground to 1-3 µm) was added to the water on the same watering days as for the control group. Quartz suspension was shaken beforehand and provided in shallow porcelain dishes once a day. Animals were deprived of food for 6 hours before water was provided, then allowed to drink *ad libitum* for 1 hour, and thereafter feeding was continued.
	Exposure concentrations (if applicable)	50 or 250 mg SiO_2/L
	Comparison group(s)	Control groups received 'clean' tap water from Beograd waterworks.
Study methods	Water quality measurement used	No information on this in paper (presumably not done)
	Water sampling methods (monitoring, surrogates)	No information on this in paper (presumably not done)
Results (for each outcome)	Definition of outcome	• Monitored for clinical signs, body weight, food consumption, and histopathology of the kidneys.
	How outcome was assessed	
	Method of measurement	Not reported
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	20/group
Statistics (if any)	Statistical method used	Details not provided in study methods.
	Details on statistical analysis	

Publication Reference: Markovic B and Arambasic MD (1971). Experimental chronic interstitial nephritis compared with endemic human nephropathy. Journal of Pathology. 103: 35-40		
	Relative risk/odds ratio, confidence interval?	Not applicable. Summary of results: • By the 2nd and 3rd month of the experiment, the animals showed clinical signs of the disease; they were losing weight progressively, they were taking less and less food, and their movements became slow and eyes sunken. • Treated animals developed interstitial type chronic renal inflammation (incidence not provided). The pathological changes are similar to those found in humans in Yugoslavia in the cases of endemic nephropathy caused by rock erosion in village communities on the banks of the lower reaches of large rivers.
Author's conclusions	Interpretation of results	• The lowest concentration of the silicate suspension that, under the conditions of the test, induced interstitial nephritis was 50 mg per litre of water; this is approaching the quantity of SiO_2 detectable in the drinking water in areas affected by endemic nephropathy, which varies, however, with the season of the year. • On the basis of this study, it may be concluded that pure SiO_2 (quartz) is nephrotoxic under certain experimental conditions. Its nephrotoxicity is caused by disintegration of quartz particles with the release of silicic acid, which under certain biochemical conditions in the kidneys becomes toxic and produces the pathological changes the authors have described.
	Assessment of uncertainty (if any)	Do not know minimum dose of the silicate suspension that would cause definite pathological effects in the kidneys experimentally.
Reviewer comments	Results included/excluded in review (if applicable)	• The study tested the effect of a quartz suspension (at 50 and 250 mg SiO_2/L) on guinea pigs, and found after 2-3 months guinea pigs developed nephropathy similar to that observed in humans in endemic nephropathy regions in Yugoslavia. • No NOAEL was identified in this study and amount of water ingested by guinea pigs (for calculation of a dose) was also not provided. • As this paper may be important for hazard characterisation, it was subjected to RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Mascarenhas et al. 2017

Publication Reference: Mascarenhas S., Mutnuri S. and Ganguly A. (2017). Deleterious role of trace elements - Silica and lead in the development of chronic kidney disease. Chemosphere 177: 239-249.		
General Information	Date of data extraction	28/05/2023
	Authors	Mascarenhas S, Mutnuri S, Ganguly A
	Publication date	2017
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes

Publication Reference: Mascarenhas S., Mutnuri S. and Ganguly A. (2017). Deleterious role of trace elements - Silica and lead in the development of chronic kidney disease. Chemosphere 177: 239-249.		
	Country of origin	India
	Source of funding	This work was financially supported by Council for Scientific and Industrial-Research(CSIR), India [Grant-no: 27(0284) 13/EMR-II].
	Possible conflicts of interest	No conflict of interest statement in paper (authors are from a University).
Study characteristics	Aim/objectives of study	To understand environmental risk-factors underlying Chronic-Kidney-Disease of Unknown-etiology (CKDu)-etiology using the Indian sub-district (Canacona) as case-study.
	Study type/design	Cross-sectional (observational study)
	Study duration	Not applicable
	Type of water source (if applicable)	Well water (used for drinking)
Population characteristics	Population/s studied	A detailed-list of Canacona sub-district's CKD-affected patients were obtained from two main hospitals in Goa-Apollo Victor hospital and Canacona Health Centre. On analysis it was found that 142 from a combined total of 180 patients were hailing from Canacona sub-district, from which 80% of the patients (n = 114) were residents of two villages - Ponsulem and Chaudi, they were grouped under study-group 1 (area of residence study-area 1). The remaining 28 patients hailing from scattered villages of the sub-district namely Cola, Poinguinim and Anvali were grouped under non-endemic study-group 2 (area of residence-study-area 2). For true-controls, volunteers from two healthy villages of the sub-district namely Molorem and Endrem were randomly chosen and grouped under study-group 3 (residence study-area 3). The sample-size for group 3 was calculated considering the prevalence of CKD in study-group one (80%) bearing a precision of 10% and confidence interval of 95% resulting in sample-size for each village to be 62 subjects with a 1:1 ratio of both sexes.
	Selection criteria for population (if applicable)	
	Subgroups reported	
	Size of study	
Exposure and setting	Exposure pathway	Drinking water
	Source of chemical/ contamination	Natural mineralogy in well water or potentially acid-mine drainage (AMD) taking place from open-quarries of the abandoned granite-mine located in close proximity to neighbouring aquifer of the CKDu-endemic region. The higher silica levels as compared to lead can be attributed to rich silica-reserves (>75% silica) and poor lead-deposits (2.5% by-weight) constituting the granitic-bedrock of CKDu-endemic-region's aquifer. The acidic groundwater on interaction with the granitic-aquifer causes excessive leaching of silica as compared to lead, which is further enhanced by Ca-Mg-deficient geochemical composition of the groundwater (as these cations [Ca/Mg] form complexes with silica reducing silica's solubility) resulting in higher silica-levels than lead.
	Exposure concentrations (if applicable)	• Study area 1: 115.5 mg/L • Study area 2: 13.9 mg/L • Study area 3: 13.52 mg/L
	Comparison group(s)	Controls in study group 3

Publication Reference: Mascarenhas S., Mutnuri S. and Ganguly A. (2017). Deleterious role of trace elements - Silica and lead in the development of chronic kidney disease. Chemosphere 177: 239-249.		
Study methods	Water quality measurement used	Silica was measured by the American Public Health Association (APHA)-ammonium-molybdate standard spectrophotometric (Shimadzu UV-1800,Tokyo, Japan) method (4500-SiO_2. C).
	Water sampling methods (monitoring, surrogates)	Since groundwater is major source of drinking-water as observed from the demographic-study, a complete hydro-geochemical analysis of groundwater of the study-regions was conducted to check for various environmental toxins. Well water sampled used for drinking by patients were collected during three seasons in 2015-2016. Samples (500 ml each) were collected in duplicates from each well in pre-cleaned high-density polypropylene bottles, one of which was acidified with 10% concentrated nitric-acid for trace-metal analysis. All samples were tightly capped and details were recorded. A total of 142 samples were collected from the endemic-region (study-area 1), 28 samples from the non-endemic region (study-area 2) and 124 samples from no-CKD prevalence region (study-area 3).
Results (for each outcome)	Definition of outcome	• Biochemical parameters, heavy metals in whole blood, and anthropometric parameters collected for CKD-cases. • The lead levels in the endemic region (study-area 1) were borderline (9.98 µg/L) compared to the 2011 WHO Guideline value and significantly higher (11-fold higher) than the non-endemic area (0.87 µg/L). Nephrotoxic heavy-metals like Cr, Cd, Hg and As were below detectable levels in the three study-areas for three sampling-periods (seasons). • Mean silica levels in the endemic study-area 1 groundwater (115.5 mg/L) were significantly higher (8-fold higher) than the non-endemic area (13.9 mg/L) and 12-fold higher than reference-source (13.52 mg/L). • Diabetes and hypertension are major risk-factors for CKD-development but this was not the case with the endemic CKDu-affected patients of the Indian sub-district (Canacona). Biochemical-analysis of their blood and anthropometric study revealed normal blood-glucose (4.6 mM) levels and blood-pressure (118/80 mmHg) as compared to higher blood-glucose (7.3 mM) and blood-pressure (123/84 mmHg) of the non-endemic CKDu-affected patients, confirming a different kind of CKD. • Authors state that the study-group 1 (endemic-group) patients also reported higher blood lead-levels as compared to borderline-levels reported in the groundwater (hydro-geochemical screening) indicating its impaired clearance from the body due to direct renal damage induced as a consequence of bioaccumulation (long half-life) in the kidney (primary target-organ of heavy-metal toxicity) associated with chronic exposure.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Unclear from the main paper
Statistics	Statistical method used	

Publication Reference: Mascarenhas S., Mutnuri S. and Ganguly A. (2017). Deleterious role of trace elements - Silica and lead in the development of chronic kidney disease. Chemosphere 177: 239-249.		
(if any)	Details on statistical analysis	The hydro-geochemical, demographic, biochemical and cytotoxicity data analysis (note cytotoxicity not described here, as these were conducted using *in vitro* studies) was accomplished using SPSS-Statistics software (Version 20.0). Differences at $p < 0.05$ were considered to be significant.
	Relative risk/odds ratio, confidence interval?	Not provided
Author's conclusions	Interpretation of results	• The high predominance of endemic CKD (mainly chronic tubulo-interstitial nephritis) in some villages of Indian sub-district (Canacona) could be an outcome of the individual or synergistic effects of prolonged exposure to high-levels of potentially nephrotoxic trace geogenic-element silica and borderline-levels of lead along with continuous consumption of Nonsteroidal Anti-inflammatory Drugs (NSAID's).
	Assessment of uncertainty (if any)	Not undertaken
Reviewer comments	Results included/excluded in review (if applicable)	• The study authors make a large claim in terms of silica exposure in groundwater (at 115.5 mg/L but not at ~13.5 mg/L) being the potential cause for CKD observed in some villages in India. However, no statistical analysis or odds ratios were calculated in this study and no correction for confounders was undertaken. The authors used the results of *in vitro* cytotoxicity assays to argue for such an association. • The reviewer considers the conclusions to be inappropriately justified. • As the paper provides potential dose-response information, it was subjected to risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

Najda et al. 1991

Publication Reference: Najda J., Gminski J., Drozdz M. and Flak A. (1991). The effect of silicon (Si) on lipid parameters in blood serum and arterial wall. Biol Trace Elem Res 31(3): 235-247.		
General Information	Date of data extraction	28/05/2023
	Authors	Najda J, Gminski J, Drozdz M, Flak A
	Publication date	1991
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	Poland
	Source of funding	Not stated.
	Possible conflicts of interest	No conflict of interest statement in paper (authors are from a Medical Academy).

Publication Reference: Najda J., Gminski J., Drozdz M. and Flak A. (1991). The effect of silicon (Si) on lipid parameters in blood serum and arterial wall. Biol Trace Elem Res 31(3): 235-247.		
Study characteristics	Aim/objectives of study	To investigate the influence of an excess of a silicon soluble compound administered orally on lipid parameters measured in serum and the arterial wall of rats.
	Study type/design	Experimental animal study
	Study duration	18 weeks with progressively increasing concentration given to test animals (6 weeks at each dose)
	Type of water source (if applicable)	Not stated
Population characteristics	Population/s studied	Wistar rats (2 months, 180g). N=60 experimental, N=40 controls
	Selection criteria for population (if applicable)	
	Subgroups reported	
	Size of study	
Exposure and setting	Exposure pathway	Oral (in drinking water)
	Source of chemical/ contamination	Reagent grade sodium metasilicate nonahydrate ($Na_2SiO_3.9H_20$— REACHIM), so stock solution contained 10.11% of silicon.
	Exposure concentrations (if applicable)	0.05% (100 mg/kg bw/d), 0.1% (200 mg/kg bw/d) or 0.2% (400 mg/kg bw/d) Si
	Comparison group(s)	N=40 controls
Study methods	Water quality measurement used	Not stated
	Water sampling methods (monitoring, surrogates)	Not stated
Results (for each outcome)	Definition of outcome	• Lipid parameters determined in serum after 6, 12 and 18 weeks into the experiment. Fresh tissue mass of aorta determined and used for lipid parameter determinations. • High Density Lipoprotein (HDL)-cholesterol and HDL-phospholipid concentrations at week 12 and 18 were significantly higher than in controls. Low Density Lipoprotein (LDL) cholesterol at the same time points was lower than in controls. • No statistical difference in parameters in the aortic walls.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	N=40 controls, n=60 treated rats
Statistics (if any)	Statistical method used	The results obtained were statistically analysed using the test for two mean values from small groups and the Student's t-test.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Authors concluded both from their findings and the literature that silicon may have antiatheromatous properties and the arterial wall is probably not the only site of silicon action.

Publication Reference: Najda J., Gminski J., Drozdz M. and Flak A. (1991). The effect of silicon (Si) on lipid parameters in blood serum and arterial wall. Biol Trace Elem Res 31(3): 235-247.		
	Assessment of uncertainty (if any)	Not done
Reviewer comments	Results included/excluded in review (if applicable)	• This study suggests a beneficial effect of silicon. Very limited parameters were investigated (no pathology or histopathology done), therefore this study provides limited information regarding the silicon dose response. • As this study is unlikely to be a key critical study for dose response assessment, it was not subjected to risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

Najda et al. 1993a

Publication Reference: Najda J., Gmiński J., Drózdz M. and Danch A. (1993). The action of excessive, inorganic silicon (Si) on the mineral metabolism of calcium (Ca) and magnesium (Mg). Biol Trace Elem Res 37(2-3): 107-114.		
General Information	Date of data extraction	28/05/2023
	Authors	Najda J, Gminski J, Drozdz M, Danch A
	Publication date	1993
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	Poland
	Source of funding	Not stated.
	Possible conflicts of interest	No conflict of interest statement in paper (authors are from a Medical Academy).
Study characteristics	Aim/objectives of study	To study the influence of oral silicon treatment on the levels of calcium and magnesium in blood serum and tissues of rats.
	Study type/design	Experimental animal study
	Study duration	18 weeks with progressively increasing concentration given to test animals (6 weeks at each dose)
	Type of water source (if applicable)	Not stated
Population characteristics	Population/s studied	Wistar rats (2 months, 180g). N=60 experimental, N=40 controls
	Selection criteria for population (if applicable)	
	Subgroups reported	
	Size of study	
Exposure and setting	Exposure pathway	Oral (in drinking water)
	Source of chemical/ contamination	Reagent grade sodium metasilicate nonahydrate (Na_2SiO_3 - $9H_20$—REACHIM), so stock solution contained 10.11% of silicon.
	Exposure concentrations (if applicable)	0.05% (100 mg/kg bw/d), 0.1% (200 mg/kg bw/d) or 0.2% (400 mg/kg bw/d) Si

Publication Reference: Najda J., Gmiński J., Drózdz M. and Danch A. (1993). The action of excessive, inorganic silicon (Si) on the mineral metabolism of calcium (Ca) and magnesium (Mg). Biol Trace Elem Res 37(2-3): 107-114.		
	Comparison group(s)	N=40 controls
Study methods	Water quality measurement used	Not stated
	Water sampling methods (monitoring, surrogates)	Not stated
Results (for each outcome)	Definition of outcome	• Samples of serum, liver, kidneys, lungs and aorta were subjected to trace element determination by AAS. • A decrease of magnesium concentration in serum was observed with accompanying elevation of registered calcaemia. Moreover, a reduction of tissue calcium levels was found with a simultaneous increase of magnesium tissue pool.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	N=40 controls, n=60 treated rats
Statistics (if any)	Statistical method used	The results obtained were statistically analysed using the test for two mean values from small groups and the Student's t-test.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• The results provide evidence for silicon involvement in mineral metabolism.
	Assessment of uncertainty (if any)	Not done
Reviewer comments	Results included/excluded in review (if applicable)	• Very limited parameters were investigated therefore this study provides limited information regarding the silicon dose response. • As this study is unlikely to be a key critical study for dose response assessment, it was excluded from further assessment and not subjected to risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

Najda et al. 1993b

Publication Reference: Najda J., Gmiński J., Drózdz M. and Zych F. (1993). The influence of inorganic silicon (Si) on pituitary-thyroid axis. Biol Trace Elem Res 37(2-3): 101-106.		
General Information	Date of data extraction	28/05/2023
	Authors	Najda J, Gminski J, Drozdz M, Zych F
	Publication date	1993
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	Poland
	Source of funding	Not stated.

Publication Reference: Najda J., Gmiński J., Drózdz M. and Zych F. (1993). The influence of inorganic silicon (Si) on pituitary-thyroid axis. Biol Trace Elem Res 37(2-3): 101-106.		
	Possible conflicts of interest	No conflict of interest statement in paper (authors are from a Medical Academy).
Study characteristics	Aim/objectives of study	To study the influence of oral silicon treatment on the levels of Thyroid Stimulating Hormone (TSH) and thyroid hormones in rats.
	Study type/design	Experimental animal study
	Study duration	18 weeks with progressively increasing concentration given to test animals (6 weeks at each dose)
	Type of water source (if applicable)	Not stated
Population characteristics	Population/s studied	Wistar rats (2 months, 180g). N=20 experimental, N=10 controls
	Selection criteria for population (if applicable)	
	Subgroups reported	
	Size of study	
Exposure and setting	Exposure pathway	Oral (in drinking water)
	Source of chemical/ contamination	Reagent grade sodium metasilicate nonahydrate (Na_2SiO_3 - $9H_20$— REACHIM), so stock solution contained 10.11% of silicon.
	Exposure concentrations (if applicable)	0.05% (100 mg/kg bw/d), 0.1% (200 mg/kg bw/d) or 0.2% (400 mg/kg bw/d) Si
	Comparison group(s)	N=10 controls
Study methods	Water quality measurement used	Not stated
	Water sampling methods (monitoring, surrogates)	Not stated
Results (for each outcome)	Definition of outcome	• TSH and other thyroid hormones determined in serum/blood. • TSH was significantly higher in treated rats than controls, whereas no statistically significant difference was observed for T3 or T4. • Neither behavioural changes between the two groups nor toxic effects of the administered compound, were observed in the course of the experiment.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	N=40 controls, n=60 treated rats
Statistics (if any)	Statistical method used	The results obtained were statistically analysed using the test for two mean values from small groups and the Student's t-test.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	The elevation of TSH suggests an action of sodium silicate on hypophysis. Silicon seems to play an important role in hormonal balance.

Publication Reference: Najda J., Gmiński J., Drózdz M. and Zych F. (1993). The influence of inorganic silicon (Si) on pituitary-thyroid axis. Biol Trace Elem Res 37(2-3): 101-106.		
	Assessment of uncertainty (if any)	Not done
Reviewer comments	Results included/excluded in review (if applicable)	• Very limited parameters were investigated therefore this study provides limited information regarding the silicon dose response. • As this study is unlikely to be a key critical study for dose response assessment, it was excluded from further assessment and not subjected to risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

Newberne and Wilson 1970

Publication Reference: Newberne P. M. and Wilson R. B. (1970). Renal damage associated with silicon compounds in dogs. Proc Natl Acad Sci U S A 65(4): 872-875.		
General Information	Date of data extraction	29/05/2023
	Authors	Newberne PM and Wilson RB
	Publication date	1970
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	USA
	Source of funding	This work was supported in part by Department of Army Contract DA-49-193-MD2560.
	Possible conflicts of interest	No conflict of interest declaration in paper.
Study characteristics	Aim/objectives of study	To report on experiments in which a number of oral preparations of various forms of silicon (silicon dioxide, aluminium silicate, sodium silicate, and magnesium trisilicate) were fed to Beagle dogs and rats of both sexes.
	Study type/design	Experimental animal study
	Study duration	4 weeks
	Type of water source (if applicable)	Not applicable and not stated
Population characteristics	Population/s studied	
	Selection criteria for population (if applicable)	
	Subgroups reported	

Publication Reference: Newberne P. M. and Wilson R. B. (1970). Renal damage associated with silicon compounds in dogs. Proc Natl Acad Sci U S A 65(4): 872-875.		
	Size of study	1) Purebred Beagles of both sexes (6 months of age, 7-9 kg); vaccinated against leptospirosis, canine distemper, and hepatitis, and conditioned for 2 weeks in the laboratory. Treated subgroups were given an approximate equivalent amount of SiO_2 (0.8 g/kg bw/d): a. Control (n=6/sex) b. Silicon dioxide (0.8 g/kg bw/day) (9 males, 8 females) c. Aluminium silicate (1.3 g/kg bw/day) (6 males, 7 females) d. Sodium silicate (2.4 g/kg bw/day) (8 males, 7 females) e. Magnesium trisilicate (1.8 g/kg bw/day) (9/sex) 2) Charles River Cesarean-Derived (CD) rats of both sexes (80-100g). 15 rats/sex were fed each compound in amounts equivalent to those fed to dogs.
Exposure and setting	Exposure pathway	Oral (via incorporation into a highly palatable diet for dogs, or a semisynthetic diet for rats) Note it is not completely clear from the study whether the administration in dogs was done by bolus capsule along with a palatable diet or mixed into the diet; according to EFSA (2018c) administration occurred via bolus dosing which suggests delivery by capsule together with the diet (also not an unusual form of administration in dog studies). SLR has relied partially on the EFSA (2018c) interpretation of this study
	Source of chemical/ contamination	Purposeful addition into diet
	Exposure concentrations (if applicable)	0 or 0.8 g/kg/d SiO_2 (i.e. ~0.37 g Si/kg bw/d)
	Comparison group(s)	Control group
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	
	How outcome was assessed	

Publication Reference: Newberne P. M. and Wilson R. B. (1970). Renal damage associated with silicon compounds in dogs. Proc Natl Acad Sci U S A 65(4): 872-875.		
	Method of measurement	• The only significant clinical abnormalities exhibited by the dogs at any point during the four-week period were polydipsia and polyuria, observed in a few animals fed sodium silicate and magnesium trisilicate. Soft faeces, discoloured by unabsorbed compound, were seen occasionally in most treated dogs. Body weight, food intake, and urinary and blood measurements were essentially normal in all dogs. • The only clinical symptoms observed in the rats were polydipsia, polyuria, and soft stools, seen intermittently in a few animals fed magnesium trisilicate or sodium silicate. All clinical chemical tests were within normal limits in rats. • Gross cortical lesions of the kidney were observed in all male dogs, and in all but one female dog fed sodium silicate. The lesions appeared to be focal, subcapsular haemorrhages but, on the cut surface, they suggested cortical infarcts. Similar lesions were seen in all animals of both sexes fed magnesium trisilicate but they were not observed in animals fed aluminium silicate or silicon dioxide. • Histopathologic studies revealed characteristic lesions in the kidneys of all dogs fed sodium silicate or magnesium trisilicate but none in any of the other groups. The nature of the lesion was the same in all cases, but severity varied from one animal to another and from one area to another within a kidney. The general impression was one of irritation of tubular epithelium followed by degenerative and regenerative changes; these alterations were accompanied by inflammatory cell infiltration into the interstitium. • There were no treatment-related histopathological lesions in any of the rats. The only departure from normal observed in an occasional rat from each group was an isolated hyaline tubular cast.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	6-9 dogs/sex/group 15 rats/sex/group
Statistics (if any)	Statistical method used	Not stated.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	Although the rat was unaffected in these experiments, the unusual lesions in the kidney of the dog suggest a basic defect in the ability of this species to metabolise or excrete these compounds and present an interesting pathologic lesion for further study.
	Assessment of uncertainty (if any)	Authors suggest further study is warranted.
Reviewer comments	Results included/excluded in review (if applicable)	

Publication Reference: Newberne P. M. and Wilson R. B. (1970). Renal damage associated with silicon compounds in dogs. Proc Natl Acad Sci U S A 65(4): 872-875.		
	Notes on study quality, e.g. gaps, methods	• The study provides important information for the hazard assessment of soluble and less soluble forms of silica. The more soluble sodium silicate and magnesium trisilicate resulted in histopathological lesions in almost all dogs (7-9/group) administered ~0.37 g Si/kg bw/d), whereas silicon dioxide and aluminium silicate did not result in any adverse effects in dogs. The same dose in rats was a NOAEL in this study. • Included in risk of bias assessment.

Pruksa et al. 2014

Publication Reference: Pruksa S., Siripinyanond A., Powell J. J. and Jugdaohsingh R. (2014). Silicon balance in human volunteers; a pilot study to establish the variance in silicon excretion versus intake. Nutr Metab (Lond) 11(1): 4.		
General Information	Date of data extraction	28/05/2023
	Authors	Pruksa S, Siripinyanond A, Powell JJ, Jugdaohsingh R
	Publication date	2014
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	UK and Thailand
	Source of funding	This study was supported by the Office of Higher Education Commission, Thailand Research Fund and core institutional funds: Medical Research Council (grant number MC_US_A090_0008/Unit Programme number U1059).
	Possible conflicts of interest	All authors declare that they have no competing interests.
Study characteristics	Aim/objectives of study	To determine the balance in excretion of silicon (faecal and urinary) vs. intake, using a single oral dose of silicic acid (28.9 mg Si) in human volunteers on a standardised diet.
	Study type/design	Human controlled trial
	Study duration	Baseline measurements 24 hours and just before administration of dose. Dose ingested within 10-15 minutes. 48-hour observation with blood and urine samples taken at various intervals.
	Type of water source (if applicable)	Ultra-high purity (UHP) water was from a water purifier (Labscan Asia Co Limited, Bangkok, Thailand).
Population characteristics	Population/s studied	14 healthy volunteers (7 males, 7 females, aged 18-23 years) recruited by advertisement on notice boards at Loei Rajabhat University, Thailand. Two subjects (one male and one female) were excluded due to fainting during blood collection at the screening stage. The remaining 12 subjects were self-reportedly healthy with normal renal function, as assessed by serum creatinine, and were not taking Si supplements and/or medicines containing Si and were not pregnant or lactating.
	Selection criteria for population (if applicable)	
	Subgroups reported	

Publication Reference: Pruksa S., Siripinyanond A., Powell J. J. and Jugdaohsingh R. (2014). Silicon balance in human volunteers; a pilot study to establish the variance in silicon excretion versus intake. Nutr Metab (Lond) 11(1): 4.		
	Size of study	The 12 subjects were divided into two groups of six, matched for age, BMI and male to female ratio. One group ingested 500 mL UHP water (Control group) and the other group 500 ml of the Si supplement solution (28.9 mg Si; Si-supplemented group).
Exposure and setting	Exposure pathway	Oral (supplement in drinking water)
	Source of chemical/ contamination	Purposefully added supplement in drinking water. The stock basic sodium silicate solution was from Lakehead University, Canada (Professor Stephen Kinrade). The Si supplement (orthosilicic acid solution, OSA) was prepared fresh, just prior to ingestion, by dilution of the stock basic sodium silicate solution (1.58 mol Si/L or 45.72 g Si/L) into UHP water and pH neutralisation to 7.2 with HCl.
	Exposure concentrations (if applicable)	0 or 28.9 mg supplemental Si (all participants received the same meals during the study, therefore Si intakes from meals were identical; Si intake from meals was ~24 mg/day)
	Comparison group(s)	Control group (0 mg supplemental Si)
Study methods	Water quality measurement used	The Si concentration in the test solution (2.06 mmol/L or 57.78 mg/L) was confirmed by inductively coupled plasma – optical emission spectrometry (ICP-OES; Perkin Optima, model 2100 DV).
	Water sampling methods (monitoring, surrogates)	-
Results (for each outcome)	Definition of outcome	Serum Si analysis confirmed the ready absorption of silicon from the orthosilicic acid solution. Mean total urinary and faecal Si excretions over the 24 h post-dose period accounted for 57 ± 9.5% and 39 ± 9.4% of the ingested dose, respectively. Thus in total 96.3 ± 5.8% of the ingested dose was recovered in faecal plus urinary excretions over the 24 h post-dose period.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	N=12 (6 treated, 6 controls)
Statistics (if any)	Statistical method used	Sample size (power) calculation was based on the available data on urinary Si excretion. No previous data existed for faecal Si excretion. A relative standard deviation (σ) of 9.4% was estimated for the variance in urinary Si and a potential difference of 20% for the excretion of urinary Si between the Si supplement and water test solutions was assumed, with 90% power at a 5% significance level. Sample size formula for the difference of two independent means was used for the calculation and six completed subjects were the minimum required for each test solution.
	Details on statistical analysis	Area under the curve (AUC) of serum Si was calculated using the linear trapezoidal rule. Due to a small number of subjects in each group, differences in serum AUC, and in urinary and faecal excretions of Si, between the two groups (Si vs. control), were analysed non-parametrically using the Mann–Whitney Rank test. Statistical analyses were two sided and a P value ≤0.05 was considered significant. SPSS for Windows version 13.0 was used.

Publication Reference: Pruksa S., Siripinyanond A., Powell J. J. and Jugdaohsingh R. (2014). Silicon balance in human volunteers; a pilot study to establish the variance in silicon excretion versus intake. Nutr Metab (Lond) 11(1): 4.		
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	In healthy subjects (presumably in Si balance), the ingestion of a soluble dose of dietary Si results in the same quantity (within analytical error) being excreted within 24 hours. It is currently not known if this all originated from the dose solution or if there was some exchange with the body Si pool but, given the low variance in these silicon balance data, isotopic studies are now merited.
	Assessment of uncertainty (if any)	Authors cannot be certain that the Si excreted in urine and faeces all originated from the ingested Si dose and that there was not some exchange with the body Si pool- as for example occurs with dietary phosphate.
Reviewer comments	Results included/excluded in review (if applicable)	• The study provides useful information regarding silicon absorption and excretion following a single oral dose (of soluble silicon in drinking water) in human volunteers. • However, as no health endpoints were investigated, this study does not inform on the dose response of silicon exposure, it was excluded from further assessment and not assessed for risk of bias.
	Notes on study quality, e.g. gaps, methods	

Rapant et al. 2015

Publication Reference: Rapant S., Fajčíková K., Cvečková V., Ďurža A., Stehlíková B., Sedláková D. and Ženišová Z. (2015). Chemical composition of groundwater and relative mortality for cardiovascular diseases in the Slovak Republic. Environ Geochem Health 37(4): 745-756.		
General Information	Date of data extraction	28/05/2023
	Authors	Rapant S, Fajcikova K, Cveckova V, Durza A, Stehlikova B, Sedlakova D, Zenisova Z
	Publication date	2015
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	Slovak Republic
	Source of funding	This research has been performed within the projects Geohealth (LIFE10 ENV/SK/000086) and Life for Krupina (LIFE12 ENV/SK/000094) which are financially supported by the EU's funding instrument for the environment: Life + programme and Ministry of the Environment of the Slovak Republic.
	Possible conflicts of interest	No conflict of interest statement was included in the paper.
Study characteristics	Aim/objectives of study	To determine which chemical elements in groundwater are most closely associated with cardiovascular disease (CVD) mortality and, simultaneously, to suggest limit concentrations (optimum, maximum allowable and minimum required), for which CVD mortality is as low as possible.

Publication Reference: Rapant S., Fajčíková K., Cvečková V., Ďurža A., Stehlíková B., Sedláková D. and Ženišová Z. (2015). Chemical composition of groundwater and relative mortality for cardiovascular diseases in the Slovak Republic. Environ Geochem Health 37(4): 745-756.		
	Study type/design	Ecological (population data)
	Study duration	Not applicable
	Type of water source (if applicable)	Groundwater
Population characteristics	Population/s studied	The Relative mortality for cardiovascular diseases (ReI) data used in this paper represent average values for the period 1994–2003 and are thus the average values for each municipality of the Slovak Republic (2883 municipalities). They were derived from the database of the Statistical Office of the Slovak Republic. The number of person-years (denominator in the calculations) was defined as the sum of all residents in each of the 2883 municipalities on 31 December of the relevant year. This varies every year since people are born, die and migrate. Military districts, where values of health indicators are skewed, were discarded.
	Selection criteria for population (if applicable)	
	Subgroups reported	
	Size of study	
Exposure and setting	Exposure pathway	Oral (drinking water)
	Source of chemical/ contamination	Groundwater
	Exposure concentrations (if applicable)	-
	Comparison group(s)	-
Study methods	Water quality measurement used	-
	Water sampling methods (monitoring, surrogates)	Source of groundwater chemical compositions is from national environmental-geochemical mapping mainly the Geochemical Atlas of the Groundwaters and environmental-geochemical maps of Slovak regions. These were complemented in particular by data from national groundwater monitoring, hydrogeochemical maps and other regional and local geochemical works. The total number of chemical analyses of groundwater was 20,339. The data from the period 1991–2010 were used. In the case when several analyses for one water source were available, the most representative chemical analysis was selected. The density of the groundwater samples was about one sample per 2.5 square kilometres (sqkm). A 1-km2 pixel (grid) map of spatial distribution of elements and components was compiled from all the input data for the entire Slovak Republic using MapInfo Professional 9.0 software. An average elemental concentration for each pixel (grid cell) was computed through the common inverse distance interpolation gridding method based on averaging ten samples that are the nearest to the pixel centre. The average value for chemicals for specific administration units (villages, districts and Slovak Republic) was then calculated as the arithmetic mean value of each pixel falling under the administration units. Pixels that intervene only partly within an administration unit were proportionally included in the calculation.
	Definition of outcome	

Publication Reference: Rapant S., Fajčíková K., Cvečková V., Ďurža A., Stehlíková B., Sedláková D. and Ženišová Z. (2015). Chemical composition of groundwater and relative mortality for cardiovascular diseases in the Slovak Republic. Environ Geochem Health 37(4): 745-756.		
Results (for each outcome)	How outcome was assessed	• Mean concentration of SiO_2 in groundwater was 18.21 mg/L (n=20,339). • Authors observed a statistical dependence between SiO_2 and RelI, which is unlikely to be causal: as SiO_2 concentrations increase, so does RelI. However, according to the authors this relationship is mediated by the relationship between Ca, Mg, Ca + Mg and RelI rates. The SiO_2 content therefore does not have a causal relationship with RelI rather, the relationship is stochastic. In epidemiological terms, this is known as collinearity. Collinearity means that within a set of observations, some of the factors are (nearly) totally predicted by the other factors. While there are statistical methods to distinguish which factor is the truly influential factor, in this study, the known biological links between Ca or Mg and RelI give plausibility to the interpretation that SiO_2 does not have a causal relationship with RelI.
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	-
Statistics (if any)	Statistical method used	For the analysis of relationships between chemical composition of the groundwater and RelI, authors used artificial intelligence—artificial neural networks (ANN). By applying ANN, the size of effects of elements in the water on RelI was determined, together with the limit values (maximum allowable or minimal required) and optimum ranges for their groundwater concentrations. The order of effects of chemicals in groundwater on RelI was determined from the value of the sensitivity coefficient s_r. RelI is influenced by those chemical elements in the water for which the average sensitivity coefficient is greater than one.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Although there was a statistical dependence of SiO_2 in groundwater with RelI, the authors concluded SiO_2 does not have a causal relationship with RelI due to the mediation by the Ca, Mg, Ca + Mg and RelI rate.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• This study provides limited information on the hazards of SiO_2 in groundwater. The study authors concluded that SiO_2 is unlikely to be causally related to RelI even though a statistical relationship between the two factors was observed. • As the paper does not provide any useful dose response information for guidance/guideline value development, it was not subjected to risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

Rondeau et al. 2009

Publication Reference: Rondeau V., Jacqmin-Gadda H., Commenges D., Helmer C. and Dartigues J. F. (2009). Aluminum and silica in drinking water and the risk of Alzheimer's disease or cognitive decline: findings from 15-year follow-up of the PAQUID cohort. Am J Epidemiol 169(4): 489-496.		
General Information	Date of data extraction	28/05/2023
	Authors	Rondeau V, Jacqmin-Gadda H, Commenges D, Helmer C, Dartigues J-F
	Publication date	2009
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	France
	Source of funding	This research was supported by the following organisations and agencies: Agence de Bassin Seine-Normandie, Aluminum Pechiney, Association pour la Recherche Bio-medicale (Institut du Cerveau), Association Recherche et Partage, Assurances–Association Generale Interprofessionnelle de Prevoyance et d'Investissement, Groupe Danone, Caisse Nationale d'Assurance Maladie des Travailleurs Salaries, Caisse Primaire d'Assurance Maladie de la Dordogne, Caisse de Prevoyance des Industries Metallurgiques, Mecaniques, Electriques et Connexes, Conseil General de la Dordogne, Conseil General de la Gironde, Conseil Regional d'Aquitaine, Caisse de Retraite Interentreprises, Direction Regionale des Affaires Sanitaires et Sociales d'Aquitaine, 2010 Media, Fondation de France, Institut National de la Sante et de la Recherche Medicale, Mutuelle Generale de l'Education Nationale, Ministere de la Recherche et de la Technologie, Mutualite Sociale Agricole de la Dordogne, Mutualite Sociale Agricole de la Gironde, Novartis Pharma, IPSEN [Institut de Produits de Synthese et d'Extraction Naturelle] Laboratories, and SCOR Insurance Group.
	Possible conflicts of interest	None declared.
Study characteristics	Aim/objectives of study	To examine associations between exposure to aluminium or silica from drinking water and risk of cognitive decline, dementia, and Alzheimer's disease among elderly subjects followed for 15 years (1988–2003) in southern France.
	Study type/design	Prospective cohort study
	Study duration	15 years
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	Persons aged 65 years or over living in 91 civil drinking-water areas in southern France.
	Selection criteria for population (if applicable)	
	Subgroups reported	

Publication Reference: Rondeau V., Jacqmin-Gadda H., Commenges D., Helmer C. and Dartigues J. F. (2009). Aluminum and silica in drinking water and the risk of Alzheimer's disease or cognitive decline: findings from 15-year follow-up of the PAQUID cohort. Am J Epidemiol 169(4): 489-496.		
	Size of study	The PAQUID Study is an ongoing prospective, population-based cohort study of the epidemiology of dementia and Alzheimer's disease in the elderly population of France. The study, beginning in 1988, initially included a community-based cohort of 3,777 elderly people aged 65 years or older who were living at home in one of 75 randomized rural or urban drinking-water areas in the administrative regions of Gironde and Dordogne in southwestern France. Subjects were randomly selected from electoral rolls and were followed up regularly between 1988 and 2004. To increase the number of exposed subjects, the authors added subjects from the Aluminum–Maladie d'Alzheimer (ALMA+) cohort. This cohort of 400 subjects was randomly selected from electoral rolls at the same time as the 10-year follow-up of the PAQUID cohort. These subjects, who were aged 75 years or over at study entry, lived at home in one of the 14 drinking-water areas in the administrative region of Dordogne in southwestern France.
Exposure and setting	Exposure pathway	Oral (drinking water)
	Source of chemical/ contamination	Not applicable
	Exposure concentrations (if applicable)	• Silica levels in tap water ranged from 4.2 mg/L to 22.4 mg/L. • In bottled water, concentrations of silica ranged from 2 mg/L to 77.6 mg/L.
	Comparison group(s)	Exposures stratified into quartiles.
Study methods	Water quality measurement used	Not stated
	Water sampling methods (monitoring, surrogates)	On the basis of information provided by the sanitary administration, authors divided the PAQUID and ALMA+ samples into 77 and 14 drinking-water areas, respectively. For each area, they computed a weighted mean of all measures of aluminium and silica using the results of chemical analyses of drinking water carried out by the sanitary administration between 1991 and 1994 (unpublished data). For evaluation of subjects' past exposure, the history of the water distribution network over the previous 10 years (1981–1991) was evaluated in the PAQUID cohort. The 8-year follow-up questionnaire given to the PAQUID cohort and the 3 following questionnaires, as well as the first and second questionnaires given to the ALMA+ cohort, included a dietary investigation that contained specific questions relating to daily consumption of tap water. The first non-missing information collected was used for each individual exposure, assuming stable daily water consumption throughout the period of observation. The statistical analyses were then based on 2 kinds of drinking water indicators for aluminium or silica: a geographic exposure measure (in mg/L) previously used in the PAQUID cohort and an individual indicator (in mg/day) that was more precise, taking daily bottled and tap water consumption into account.
Results (for each outcome)	Definition of outcome	
	How outcome was assessed	

Publication Reference: Rondeau V., Jacqmin-Gadda H., Commenges D., Helmer C. and Dartigues J. F. (2009). Aluminum and silica in drinking water and the risk of Alzheimer's disease or cognitive decline: findings from 15-year follow-up of the PAQUID cohort. Am J Epidemiol 169(4): 489-496.		
	Method of measurement	• Assessment of intellectual functioning included an evaluation of global mental status (the Mini-Mental State Examination (MMSE)) and a battery of other tests. At the end of the visit, the psychologist systematically completed a standardised questionnaire designed to obtain information on Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised criteria for dementia. A senior neurologist subsequently saw subjects who met these criteria at home to confirm and complete the diagnosis of dementia, to apply the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for Alzheimer's disease, and to calculate the Hachinski score for vascular dementia. • Mean consumption of drinking water was 0.94 L/day (standard deviation, 0.49). • Silica levels in tap water ranged from 4.2 mg/L to 22.4 mg/L and were inversely related to aluminium concentrations, but this negative correlation was weak (Pearson correlation coefficient = -0.18; P = 0.13). In bottled water, concentrations of silica ranged from 2 mg/L to 77.6 mg/L. • Neither individual intake of silica nor geographic exposure was significantly associated with cognitive function. • An increase of 10 mg/day in silica intake was associated with a reduced risk of dementia (adjusted relative risk (RR) = 0.89, P = 0.036) in one model.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Among the 4,177 subjects (3,777 from the PAQUID cohort and 400 from the ALMA+ cohort) who initially agreed to participate, 207 with prevalent dementia were excluded. The current study was restricted to the 1,925 subjects (among the 3,970 who were non-demented at their first visit) in 91 geographic areas who had non-missing values for daily consumption of aluminium or silica in drinking water and for adjustment covariates. Subjects from the PAQUID cohort who were lost to follow-up or died before the eighth year of follow-up had no measure of water consumption and were excluded from the study.
Statistics (if any)	Statistical method used	Analyses of cognitive decline were performed using a random-effects linear regression model, including a subject-specific random intercept and slope to account for intrasubject correlation.

Publication Reference: Rondeau V., Jacqmin-Gadda H., Commenges D., Helmer C. and Dartigues J. F. (2009). Aluminum and silica in drinking water and the risk of Alzheimer's disease or cognitive decline: findings from 15-year follow-up of the PAQUID cohort. Am J Epidemiol 169(4): 489-496.		
	Details on statistical analysis	Since the distribution of MMSE scores was not normal, authors analysed the square root of the number of errors according to time. Besides the time variable representing the number of years after the initial visit, a binary indicator for the initial visit was introduced to account for a first-pass effect, possibly due to stress. Aluminium was considered as a quantitative variable or as a categorical variable. A binary variable was chosen with the threshold of 0.1 mg/L already used in previous ecological studies, or 0.1 mg/day for individual exposure. Four classes were also used according to the 3 tertiles (on subjects) under 0.1 mg/day and the category at or above 0.1 mg/day. Silica was considered as a quantitative variable or as a binary variable with 11.25 mg/L as the cutoff for geographic exposure (the median in the sample) and 10.55 mg/day as the cutoff for individual exposure (the median daily intake in the sample), or in 4 quartiles. They adjusted for the following potential confounders: educational level, wine consumption, place of residence (rural vs. urban), and cohort (PAQUID or ALMA+). Analyses of the risk of dementia or Alzheimer's disease were performed using a Cox proportional hazards model with delayed entry to estimate relative risks and to adjust for covariates. Age was used as the basic time scale in the analysis, so the risks of dementia or Alzheimer's disease were adjusted nonparametrically for age. A stratified analysis for gender was performed.
	Relative risk/odds ratio, confidence interval?	Dementia: • Model 4: RR 0.89 (0.8, 0.98) • Model 5: RR 0.89 (0.81, 0.99) • Model 6: RR 0.89 (0.81, 0.99) Alzheimer's disease: • Model 4: RR 0.88 (0.79, 0.99) • Model 5: RR 0.89 (0.79, 1.0) • Model 6: RR 0.88 (0.79, 0.99)
Author's conclusions	Interpretation of results	• The analysis did not show any evidence of silica intake being associated with the evolution of cognitive function; however, it showed an inverse association between silica intake from drinking water and the risk of dementia, or more specifically Alzheimer's disease.

Publication Reference: Rondeau V., Jacqmin-Gadda H., Commenges D., Helmer C. and Dartigues J. F. (2009). Aluminum and silica in drinking water and the risk of Alzheimer's disease or cognitive decline: findings from 15-year follow-up of the PAQUID cohort. Am J Epidemiol 169(4): 489-496.		
	Assessment of uncertainty (if any)	• Although authors adjusted for several potentially confounding factors, the possibility of residual confounding cannot be completely excluded. Authors thus adjusted for several individual factors, such as age, gender, wine consumption, educational level, and place of residence (which is potentially associated with bottled water consumption). • Subjects drinking only bottled water may have different exposures, since they are not exposed to aluminium from drinking water and can be more exposed to silica (if the bottled water contains high levels of silica). The authors repeated the main analyses after excluding those persons. In the dementia analysis in the PAQUID sample (749 subjects excluded out of 1,677), the effect of aluminium remained equivalent, but the effect of silica was no longer significant (RR =1.04, P =0.13). • Further studies are needed to settle the debate over the link between aluminium or silica in drinking water and neurologic disorders and cognitive impairment. Ideally, in such studies individual data on drinking water exposure and other relevant risk factors would be collected for assessment of this potential risk.
Reviewer comments	Results included/excluded in review (if applicable)	• This large prospective cohort study found no association for silica exposure in drinking water or bottled water (up to a concentration of 22.4 mg/L in tap water, 77.6 mg/L in bottled water) and cognitive decline, dementia, and Alzheimer's disease in France. • The study has some strengths in terms of size, long follow-up period, and individual exposure data. • It was included in risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

Takizawa et al. 1988

Publication Reference: Takizawa Y., Hirasawa F., Noritomi E., Aida M., Tsunoda H. and Uesugi S. (1988). Oral ingestion of syloid to mice ande rats and its chronic toxicity and carcinogenicity.		
General Information	Date of data extraction	29/05/2023
	Authors	Takizawa Y, Hirasawa F, Noritomi E, Aida M, Tsunoda H, Uesugi S
	Publication date	1988
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	Japan
	Source of funding	No declaration of funding provided in paper.
	Possible conflicts of interest	No conflict of interest declaration in paper (authors are from a University).

Publication Reference: Takizawa Y., Hirasawa F., Noritomi E., Aida M., Tsunoda H. and Uesugi S. (1988). Oral ingestion of syloid to mice ande rats and its chronic toxicity and carcinogenicity.		
Study characteristics	Aim/objectives of study	To establish the safety of silicon for use in food as an anti-caking agent for human consumption by characterising and evaluating the chronic oral, long-term toxicity of SYLOID (food grade micronized silica) in rodents. In addition, several carcinogenic studies were carried out as a preliminary test.
	Study type/design	Experimental animal study
	Study duration	93 consecutive weeks in mice (sacrificed at 6, 12, and 24 months) 103 consecutive weeks in rats (sacrificed at 6, 12 and 21 months)
	Type of water source (if applicable)	Not applicable (tap water was available *ad libitum*)
Population characteristics	Population/s studied	$B_6C_3F_1$ mice (16-27.3g) and Fisher rats (92-150g) (both 5 weeks of age at start of study). Total size of study = 320 for each study (160/sex) Each dose group = n=40-41/sex/group (female control mice = 38)
	Selection criteria for population (if applicable)	
	Subgroups reported	
	Size of study	
Exposure and setting	Exposure pathway	Oral (via feed)
	Source of chemical/ contamination	Purposeful addition into diet. SYLOID 244 (Fuji Davison Chemical Ltd, Japan), a fine white silica powder with chemical composition SiO_2 x H_2O.
	Exposure concentrations (if applicable)	0, 1.25, 2.5 or 5% SYLOID in diet (i.e. mice: ~0; 1.0-2.57; 1.82-3.85; 3.95-13.31 g/kg bw/d) (i.e. rats: ~0; 0.4-0.75; 0.83-1.46; 1.78-3.21 g/kg bw/d) Note EVM (2003) indicate in mice the doses were equivalent to 1,900 – 7,500 mg/kg bw silica or 900 to 3500 mg silicon. In rats, EVM (2003) states the top dose is equivalent to 2,500 mg Si/kg bw/d.
	Comparison group(s)	Control group
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	
	How outcome was assessed	

Publication Reference: Takizawa Y., Hirasawa F., Noritomi E., Aida M., Tsunoda H. and Uesugi S. (1988). Oral ingestion of syloid to mice ande rats and its chronic toxicity and carcinogenicity.		
	Method of measurement	• No significant treatment-related effects were seen at any dose on mortality, body weight, food consumption, clinical signs, clinical laboratory examinations, gross or histopathology. The occasional presence of some neoplasms did not reveal any consistent, dose-related trends in any group. • In mice, tumours attributed to the treatment of SYLOID were found in the haematopoietic organs, particularly malignant lymphoma/leukaemia, which occurred in 7/20 (35%) in the female groups of the 2.5% dosage group as opposed to 2/16 (12.5%) in controls. The results of the Cochran-Armitage test for positive dose-related trends in the incidence of tumours were not significant. • In rats, the incidence of tumours showed no significant differences between the control and treated groups (with controls frequently having higher incidences, but not significantly so).
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	N=~40/sex/dose group
Statistics (if any)	Statistical method used	The mean and standard deviations of various measured parameters were calculated for each dose group. The significant difference between the control and the compound-treated groups was tested by using Student's t-analysis variance test. The chi-square test of significance ($p<0.05$) by Mantel-Hanszel was employed to compare the survival date exclusive of sacrificed specimens. Prevalence rates were cited as percentages of tumour groups and non-tumour groups in cases of post-mortem examination. The significance of differences between the two means of prevalence was tested by using Fisher's exact test for fourfold tables. The percentages of the frequencies of tumour in specific tissues were analysed by using the following technique: The Cochran-Armitage test for linear trend in proportion with continuity correction.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• The authors concluded these results suggest that the use of SYLOID as an anti-caking agent is safe for human consumption.
	Assessment of uncertainty (if any)	Not stated.
Reviewer comments	Results included/excluded in review (if applicable)	• This study is likely a key critical study informing the toxicity of dietary silica as it is a chronic/carcinogenicity study conducted in both mice and rats. Doses of SYLOID were provided in the study, but not doses of Si. Based on the doses reported by EVM (2003), this study provides NOAELs of 2,500 mg Si/kg/d in rats and 3,500 mg Si/kg/d in mice (top dose tested, no treatment-related adverse effects observed). • This study was subjected to risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

Willhite et al. 2012

Publication Reference: Willhite C. C., Ball G. L. and McLellan C. J. (2012). Total allowable concentrations of monomeric inorganic aluminum and hydrated aluminum silicates in drinking water. Crit Rev Toxicol 42(5): 358-442.		
General Information	Date of data extraction	29/05/2023
	Authors	Willhite CC, Ball GL, McLellan CJ
	Publication date	2012
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	USA
	Source of funding	National Sanitation Foundation (NSF) International is a private not-for-profit public health and safety certification organisation. NSF International receives income from the sale of services to private and public entities. NSF International provided the sole financial and administrative support for conduct of the present assessment.
	Possible conflicts of interest	The authors' affiliation is NSF International and the review was written during their normal course of employment. The authors submitted the manuscript to the NSF International Health Advisory Board for review as noted in the Acknowledgments. However, the contents and writing of the final version of the paper are the sole responsibility of the authors. No conflict of interest declared.
Study characteristics	Aim/objectives of study	To derive total allowable concentrations for certain water-soluble inorganic aluminium (Al) compounds (including chloride, hydroxide, oxide, phosphate and sulfate) and for the hydrated Al silicates (including attapulgite, bentonite/montmorillonite, illite, kaolinite) in drinking water. The study summaries provided here focuses on the Al silicates, in case there is relevant information for silicates themselves. The review itself is focused on the toxicity of Al.
	Study type/design	Review
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	
	Size of study	
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/ contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable

Publication Reference: Willhite C. C., Ball G. L. and McLellan C. J. (2012). Total allowable concentrations of monomeric inorganic aluminum and hydrated aluminum silicates in drinking water. Crit Rev Toxicol 42(5): 358-442.		
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	
	How outcome was assessed	

	Method of measurement	• Attapulgite is a combination of aluminium oxide, silicon dioxide and magnesium oxide complexed as the Al silicate. Common naturally occurring Al silicates used in the water purification and brewing industries include bentonite and zeolite. • There are two major classes of clay: allophane (amorphous) and crystalline. Within the crystalline clays, there are four sub-types: two-layer, three-layer, regular mixed-layer, and chain structure. A common two-layer type is represented by kaolinite; common three-layer types are represented by montmorillonite and illite; and the chain-structure type is represented by attapulgite. • By and large, the greatest hazard associated with acute ingestion of attapulgite, bentonite, illite or kaolin is intestinal obstruction. Physical expansion of clays as they absorb water (to 12–15 x their dry bulk volume to form thixotrophic gels) accounts for their acute action in the large bowel. • An aqueous suspension of 'activated' (acid-treated) attapulgite has been used for decades in symptomatic treatment of diarrhoea. The usual initial dose in adults ranges from 1500 mg to 4000 mg. In a single 24-hour period, the maximum recommended adult dose is 9000 mg (130 mg/kg) and that for young children (3–6 years) is 2250 mg (225 mg/kg). Kaolin is also a traditional antidiarrhoeal and its recommended adult maximum daily dose is 262 g (3740 mg/kg). • In a 90-day randomised, double-blind, placebo-controlled Phase II clinical trial, dietary Ca montmorillonite was administered in capsules to 180 healthy male and female volunteers (age 18-58) at 0, 1.5, or 3 g/day (0, 20 or 40 mg/kg bw/d). There were no significant differences in haematology, electrolytes or liver and kidney function. Nausea, diarrhoea, heartburn and dizziness rated as "mild" to "moderate" were registered by ~0.5% of participants in all three groups, but the numbers of complaints were not significantly different across groups and there was no dose-dependent trend in numbers of complaints. All serum biochemical indices were within their normal physiological ranges. • 50% bentonite in the diet of mice resulted in choline deficiency apparently due to its properties as a base-exchange silicate and adsorption of both organic and inorganic cations. • Male and female Sprague–Dawley rats were fed 0, 0.25, 0.5, 1.0 or 2.0% (0, 2500, 5000, 10,000 or 20,000 ppm) Ca montmorillonite clay for 28 weeks. The daily clay consumption corresponded to 75, 150, 300 and 600 mg/kg-day. No signs of systemic toxicity were observed even at the top dose. • The clinical accounts of clay ingestion show that chronic, high doses can lead to reversible muscle weakness, erythrocyte hypochromia, microcytosis, hypokalaemia and skeletal muscle inflammation (myositis). The toxicity of ingested Al silicates is due to the comparatively poor nutritional quality of the diet and reduced nutrient bioavailability.

Publication Reference: Willhite C. C., Ball G. L. and McLellan C. J. (2012). Total allowable concentrations of monomeric inorganic aluminum and hydrated aluminum silicates in drinking water. Crit Rev Toxicol 42(5): 358-442.		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• It is clear that humans can tolerate very high oral exposures to montmorillonite clays without serious adverse health effects. • The authors derived a reference dose for the Al content of the hydrated Al silicates from the NOAEL identified in the 28-week dietary study conducted in male and female Sprague-Dawley rats fed 2500 – 20,000 ppm Ca montmorillonite (Afriyie-Gyawu et al. 2005).
	Assessment of uncertainty (if any)	Not applicable
Reviewer comments	Results included/excluded in review (if applicable)	• The review focused on the toxicity of Al; part of the review included consideration of Al in Al silicates. • This helped identify a potentially relevant experimental animal study with Ca montmorillonite (Novasil clay). However, the amount of Si present in the Novasil clay could not be readily found in the open literature. • Although this provides little information with respect to the toxicity of Si *per se*, it provides support that Si in montmorillonite clays are of relatively low toxicity. • The review itself was excluded from further assessment, but was used to help identify additional studies.
	Notes on study quality, e.g. gaps, methods	

Wolterbeek et al. 2015

Publication Reference: Wolterbeek A., Oosterwijk T., Schneider S., Landsiedel R., de Groot D., van Ee R., Wouters M. and van de Sandt H. (2015). Oral two-generation reproduction toxicity study with NM-200 synthetic amorphous silica in Wistar rats. Reprod Toxicol 56: 147-154.		
General Information	Date of data extraction	29/05/2023
	Authors	Wolterbeek A, Oosterwijk T, Schneider S, Landsiedel R, de Groot D, van Ee R, Wouters M, van de Sandt H
	Publication date	2015
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	The Netherlands and Germany

Publication Reference: Wolterbeek A., Oosterwijk T., Schneider S., Landsiedel R., de Groot D., van Ee R., Wouters M. and van de Sandt H. (2015). Oral two-generation reproduction toxicity study with NM-200 synthetic amorphous silica in Wistar rats. Reprod Toxicol 56: 147-154.		
	Source of funding	Sponsored by the European Chemical Industry Council Long-range Research Initiative (CEFIC-LRI N3 project) and was monitored by Monika Maier Ph.D., Evonik Industries AG, Hanau, Germany on behalf of the Association of Synthetic Amorphous Silica Producers (ASASP), a CEFIC Sector group.
	Possible conflicts of interest	The authors declare there are no conflicts of interest.
Study characteristics	Aim/objectives of study	To perform a two-generation reproduction toxicity study according to current Organisation for Economic Co-operation and Development (OECD) guideline 416 and to examine the possible effects of synthetic amorphous silica (SAS) on the reproductive performance of rats and on the growth and development of the offspring into adulthood for two consecutive generations. Note SAS is a nanostructured material and a form of SiO_2 produced for decades without significant changes in its physicochemical properties. SAS is applied in a wide variety of technological applications and consumer products. Aggregates have external dimensions typically above 100 nm (pyrogenic, precipitated, gel). SAS powder is placed on the market as micron-sized agglomerates with an internal structure in the nanoscale. Therefore this study may not be entirely relevant to the forms of silica that may arise from silicon brasses.
	Study type/design	Experimental animal study
	Study duration	Two generations
	Type of water source (if applicable)	Water from public supply was available *ad libitum* (test item administered by oral gavage).
Population characteristics	Population/s studied	116 male and 116 female Wistar outbred (Crl:WI(Han)strain) rats (4-5 weeks of age). Male animals were dosed during a 10-week premating period and during mating and up to the day before sacrifice. Female animals were dosed during a 10-week premating period and during mating, gestation and lactation up to postnatal day 21. Selected F1-generation pups were dosed by gavage from postnatal day 22 until the day prior to sacrifice.
	Selection criteria for population (if applicable)	
	Subgroups reported	
	Size of study	
Exposure and setting	Exposure pathway	Oral (via gavage)
	Source of chemical/ contamination	NM-200 Synthetic Amorphous Silica (batch PR-A-2) supplied by Joint Research Centre (Ispra, Italy) with the following characteristics: EINECS No. 231-545-4, CAS numbers 7631-86-9 (old general CAS number for silica including synthetic amorphous silica) and 112945-00-8 (CAS number for precipitated synthetic amorphous silica) and the purity was 96.5% (silicon dioxide content as SiO_2).
	Exposure concentrations (if applicable)	0, 100, 300 or 1000 mg/kg bw/day.
	Comparison group(s)	Control group
Study methods	Water quality measurement used	Not applicable

Publication Reference: Wolterbeek A., Oosterwijk T., Schneider S., Landsiedel R., de Groot D., van Ee R., Wouters M. and van de Sandt H. (2015). Oral two-generation reproduction toxicity study with NM-200 synthetic amorphous silica in Wistar rats. Reprod Toxicol 56: 147-154.		
	Water sampling methods (monitoring, surrogates)	Not applicable Once weekly, until completion of the dosing period of the study, seven bottles per dosing group were prepared, each containing the appropriate amount of NM-200 and stored at ambient temperature in the dark under N2. On each subsequent day, the required amount of vehicle (0.5% v/v of MHPC in Ultrapure water) was added to achieve concentrations of 0, 10, 30 and 100 mg/ml NM-200 and stirred on a magnetic stirrer (approximately 900 rpm) for at least 60 min. All samples were continuously stirred under the same conditions during the entire daily administration period in order to maintain the homogeneity of the NM-200 in the vehicle. At various weeks during the study samples were taken from each of the dosing formulations for analytical investigations of the hydrodynamic diameter of the SiO_2 particles using Dynamic Light Scattering (DLS) technique.
Results (for each outcome)	Definition of outcome How outcome was assessed Method of measurement	• The mean hydrodynamic diameter of the SiO_2 particles in the 10 mg/ml study samples varied between 1076 and 1664 nm and for the 30 mg/ml study samples between 876 and 1216 nm, respectively. The measured size of the 100 mg/ml study samples appeared to be the smallest (409–703 nm) but due to the high concentration of the particles in the samples they were sedimentated and aggregated. • No adverse effects on reproductive performance of rats or on the growth and development of the offspring into adulthood for two consecutive generations. No test item related effects were observed on clinical signs, mortalities, body weight and food consumption. Furthermore, no effects were observed on fertility and reproductive parameters including the mating, fertility, fecundity and gestation indices, pre-coital and gestation times, pre- and post-implantation losses and sex ratios. No oestrous cycle irregularities were observed and all sperm parameters measured were similar among the various groups. No treatment related effects were observed on any of the development parameters including pup viability indices, pup weights, pup organ weights and the sexual maturation measurements on testes descending, preputial separation and vaginal opening. • The NOAEL was 1,000 mg/kg bw/day.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Four groups of 28 rats/sex/group (one was allocated to controls). On postnatal day 4, litters of more than 8 pups were adjusted by culling extra pups by random selection to yield, as nearly as possible, four males and four females per litter. On postnatal day 21, 28 rats/sex/group were selected at random from as many litters as possible to produce the next generation.
Statistics (if any)	Statistical method used Details on statistical analysis	The statistical tests used to analyse all the parameters measured in this study are described in the legends of the Tables showing the summarising data. They included standard methods such as the Kruskal-Wallis and Mann-Whitney U test, ANOVA followed by Dunnett's multiple comparison test, and chi-squares test.

Publication Reference: Wolterbeek A., Oosterwijk T., Schneider S., Landsiedel R., de Groot D., van Ee R., Wouters M. and van de Sandt H. (2015). Oral two-generation reproduction toxicity study with NM-200 synthetic amorphous silica in Wistar rats. Reprod Toxicol 56: 147-154.		
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Under the conditions of this study, administration of synthetic amorphous silica NM-200 during two generations at concentrations up to 1000 mg/kg body weight/day had no effects on reproduction of the parental F0 and F1 generations animals nor on the development of the F1 and F2 pups, nor on the sexual maturation of the F1 weanlings. Based on the results of the present study the NOAEL was established at 1000 mg/kg body weight per day. • This lines up well with another 90-day toxicity study with colloidal silica, in which no treatment-related effects were observed in rats which were dosed by gavage with 500, 1000 and 2000 mg/kg/d of nano silica of 20 and 100 nm.
	Assessment of uncertainty (if any)	Not stated.
Reviewer comments	Results included/excluded in review (if applicable)	• Although SAS is a nanostructured material and a form of SiO_2, aggregates have external dimensions typically above 100 nm. Therefore, this study may not be entirely relevant to the forms of silica that may arise from silicon brasses but has been included because the test item characterisation has shown the diameter of the SiO_2 particles to be >100 nm. • As it provides dose response information, it has been included for risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

Yoo et al. 2022

Publication Reference: Yoo N. K., Youn S. M. and Choi S. J. (2022). Oral Toxicokinetics, Tissue Distribution, and 28-Day Oral Toxicity of Two Differently Manufactured Food Additive Silicon Dioxides. Int J Mol Sci 23(7).		
General Information	Date of data extraction	29/05/2023
	Authors	Yoo N-K, Youn S-M, Choi, S-J
	Publication date	2022
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	Korea
	Source of funding	This research was funded by a grant (20182MFDS404) from the Ministry of Food and Drug Safety in 2022, by a National Research Foundation of Korea (NRF) grant funded by the Korean government (MIST) (No. 2021R1A2C2007192), and partly by a research grant from Seoul Women's University (2022-0062).
	Possible conflicts of interest	The authors declare there are no conflicts of interest.

Publication Reference: Yoo N. K., Youn S. M. and Choi S. J. (2022). Oral Toxicokinetics, Tissue Distribution, and 28-Day Oral Toxicity of Two Differently Manufactured Food Additive Silicon Dioxides. Int J Mol Sci 23(7).		
Study characteristics	Aim/objectives of study	To evaluate oral toxicokinetics of two differently manufactured synthetic amorphous silica (SAS) particles, fumed SAS and precipitated SAS after a single-dose administration in rats. The tissue distribution and oral toxicity of both SAS particles were also assessed following 28-day repeated administration in rats to investigate the relation between the toxicokinetics and oral toxicity of SAS particles, depending on manufacturing methods. The description herein focuses on the toxicology findings of the 28-day repeated oral toxicity study. Although the primary particles in the SAS used for the study are in the nano-size range, the study was still included as being potentially relevant as high aggregate formation was observed in both cases (>100 nm in diameter).
	Study type/design	Experimental animal study
	Study duration	28 days
	Type of water source (if applicable)	Not applicable (water given *ad libitum*, exposure to test material was via gavage)
Population characteristics	Population/s studied	Sprague-Dawley rats (5 weeks old). N=5 female rats/group administered 0 or 2000 mg/kg of fumed SAS or precipitated SAS via oral gavage (in distilled water)
	Selection criteria for population (if applicable)	
	Subgroups reported	
	Size of study	
Exposure and setting	Exposure pathway	Oral (via gavage)
	Source of chemical/ contamination	Food-grade fumed SAS (AEROSIL® 200F) and precipitated SAS (SIPERNAT® 22S) were obtained from Evonik Industries AG (Essen, NRW, Germany). SAS particles were suspended in distilled water to designed concentrations (5, 30, and 200 mg/mL) and stirred for 30 min, followed by sonication for 15 min on the day of experiments.
	Exposure concentrations (if applicable)	0 or 2,000 mg/kg/d
	Comparison group(s)	Control group
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	
	How outcome was assessed	

Publication Reference: Yoo N. K., Youn S. M. and Choi S. J. (2022). Oral Toxicokinetics, Tissue Distribution, and 28-Day Oral Toxicity of Two Differently Manufactured Food Additive Silicon Dioxides. Int J Mol Sci 23(7).		
	Method of measurement	• Precipitated SAS showed higher oral absorption than fumed SAS, but the oral absorption of both SAS particles was low (<4%), even at 2000 mg/kg. • Both SAS particles, at a high dose (2000 mg/kg), were accumulated in the liver after repeated administration for 28 days, but the increased concentrations returned to normal levels at 29 days, the first day of the recovery period. A higher distribution level of precipitated SAS than fumed SAS and decomposed particle fates of both SAS particles were found in the liver at 28 days. No significant toxicological findings were observed after 28-day oral administration, suggesting their low oral toxicity.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	5 female rats/group
Statistics (if any)	Statistical method used	Data were presented as means ± standard deviations. Statistical significance was determined by using the SPSS (version 19.0, SPSS Inc., Chicago, IL, USA) or SAS (version 9.4, SAS Institute Inc., Cary, NC, USA). A one-way ANOVA test was performed for data on oral toxicokinetics, body weight, feed intake, and water consumption. A t-test was performed for organ weights and haematological and serum biochemical values. Statistical significance was accepted for p-values of <0.05.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• The repeated oral toxicity study for 28 days revealed no significant toxicological findings caused by both SAS particles. Hence, the NOAEL values of SAS particles were more than 2000 mg/kg, suggesting their low oral toxicity. • It can be, therefore, concluded that different manufacturing methods of SAS can affect oral toxicokinetics and tissue distribution, but not oral toxicity.
	Assessment of uncertainty (if any)	Authors indicates as a next step an investigation into excretion pathways, kinetics, fates and chronic oral toxicity of SAS is required.
Reviewer comments	Results included/excluded in review (if applicable)	• Although SAS is a nanostructured material and a form of SiO_2, aggregates have external dimensions typically above 100 nm. Therefore, this study may not be entirely relevant to the forms of silica that may arise from silicon brasses but has been included because the test item characterisation has shown the diameter of the SiO_2 particles to be >100 nm. • 28-day oral NOAEL = 2,000 mg/kg/d • As it provides dose response information, it has been included for risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

APPENDIX D

Risk of Bias Tables

Austin 1978

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Experimental Animal Studies greyed out.

Study ID: Austin 1978 **Study Type: Experimental Animal (EA)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	Yes	There is insufficient information provided about how subjects were allocated to study groups and, for beagles and monkeys, there is indirect evidence that there was a lack of a concurrent control group as only one animal was tested.	+
2.	Allocation concealment	Yes	There is insufficient information provided about allocation to study groups (NR)	NR
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	No	There is indirect evidence that the same vehicle was used in control and experimental animals AND identical non-treatment-related experimental conditions are assumed if authors did not report differences in housing or husbandry.	-
6.	Blinding of researchers during study?	Unknown	NR: There is insufficient information provided about blinding to study groups during the study	NR
	Attrition/Exclusion Bias			
7.	Missing outcome data	Yes	NR (i.e. there is insufficient information provided about loss of animals)	NR
	Detection Bias			
8.	Exposure characterisation	Unknown	NR: There is insufficient information provided about the validity of the exposure assessment method (i.e. purity of substances used).	NR
9.	Outcome assessment	Yes	NR: There is insufficient information provided about blinding of outcome assessors.	NR
	Selective Reporting Bias			
10.	Outcome reporting	Yes	Indirect evidence that not all of the study's measured outcomes have been reported.	+
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Burton et al. 1980

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cross-Sectional Studies greyed out.

Study ID: Burton et al. 1980 **Study Type: Cross-sectional (CrSe)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	Unknown	NR: There is insufficient information provided about the comparison group	NR
	Confounding bias			
4.	Confounding (design/analysis)	No	There is evidence that appropriate adjustments were made for known confounders, but it is uncertain whether all potential covariates have been accounted for.	-
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses (i.e. no subjects appear to have been excluded since the study is based on population mortality rates from cancer).	-
	Detection Bias			
8.	Exposure characterisation	No	Exposure (i.e. measurement of concentration in drinking water) was assessed using less-established methods that directly measure exposure and are validated against well-established methods.	--
9.	Outcome assessment	No	It is deemed that the outcome assessment methods used would not appreciably bias results as the outcome is not subjective (i.e. death from cancer)	-
	Selective Reporting Bias			
10.	Outcome reporting	Yes	NR: There is insufficient information provided about selective outcome reporting.	NR
	Other Sources of Bias			

11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	Yes	It is unclear from the publication whether statistical analysis used was appropriate, as no normality tests appear to have been conducted. In addition, the data do not appear to have been adjusted for many socioeconomic and lifestyle factors which could also influence outcome.	++

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Dobbie and Smith 1982

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Experimental Animal Studies greyed out.

Study ID: Dobbie and Smith 1982 **Study Type: Experimental Animal (EA)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	Unknown	NR: There is insufficient information provided about how subjects were allocated to study groups	NR
2.	Allocation concealment	Unknown	NR: There is insufficient information provided about allocation to study groups	NR
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	No	There is direct evidence that the same vehicle was used in control and experimental animals and identical non-treatment-related experimental conditions are assumed as authors did not report differences in housing or husbandry.	-
6.	Blinding of researchers during study?	Unknown	NR: There is insufficient information provided about blinding to study groups during the study.	NR
	Attrition/Exclusion Bias			
7.	Missing outcome data	Unknown	NR (i.e. there is insufficient information provided about loss of animals)	NR
	Detection Bias			
8.	Exposure characterisation	Unknown	NR: There is insufficient information provided about the validity of the exposure assessment method (i.e. purity of substances used).	NR
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods (i.e. deemed valid and reliable but not the gold standard) and assessed at the same length of time after initial exposure in all study groups and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (more likely to apply to objective outcome measures).	-

	Selective Reporting Bias			
10.	Outcome reporting	No	Indirect evidence that all of the study's measured outcomes have been reported; selective reporting would not appreciably bias results.	-
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Gloxhuber et al. 1983

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Experimental Animal Studies greyed out.

Study ID: Gloxhuber et al. 1983 **Study Type: Experimental Animal (EA)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	Yes	NR: there is insufficient information provided about how subjects were allocated to study groups.	NR
2.	Allocation concealment	Yes	NR: there is insufficient information provided about allocation to study groups.	NR
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	No	There is direct evidence that same vehicle was used in control and experimental animals, AND there is direct evidence that non-treatment-related experimental conditions were identical across study groups (i.e., the study report explicitly provides this level of detail).	--
6.	Blinding of researchers during study?	No	It is deemed that lack of adequate blinding during the study would not appreciably bias results, as it was not possible to undertake blinding due to requirement for feed and water renewal. Outcome measures were objective rather than subjective, so inadequate blinding is unlikely to appreciably bias results.	-
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	It is deemed that the proportion (of animals) lost would not appreciably bias results, as it was similar across test and control groups.	-

	Detection Bias			
8.	Exposure characterisation	Yes	NR: there is insufficient information provided about the validity of the exposure assessment method, but no evidence for concern.	NR
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods (i.e. deemed valid and reliable), AND assessed at the same length of time after initial exposure in all study groups, and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results, as results were objective outcome measures.	-
	Selective Reporting Bias			
10.	Outcome reporting	Yes	There is indirect evidence that not all of the study's measured outcomes outlined in the protocol, methods, abstract and/or introduction (that are relevant for the evaluation) have been reported (e.g. authors state the paper only provides an extract of the clinical and biochemical findings, but further data from this study can be obtained on request from the authors).	+
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or Not Reported (NR)	+/NR	Definitely high risk of bias (++)	++

Hagman et al. 2020

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Human Controlled Trials (HCT) greyed out.

Study ID: Hagman et al. 2020 **Study Type: Human Controlled Trial (HCT)**	**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q			
	Selection bias		
1.	Randomization	No	Paper only has two groups, one of healthy weight and one of obese weight. Randomisation not applicable in this study.	-
2.	Allocation concealment	Yes	This was a single-blinded uncontrolled study. There is direct evidence that at the time of recruitment research personnel (but not subjects) knew what study group subjects were allocated to.	+
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			

4.	Confounding (design/analysis)	N/A	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	Yes	The paper states that the study was single-blinded (only subjects, but not research personnel were blinded). Thus there was no blinding of research personnel.	++
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is direct evidence that there was no loss of subjects during the study and outcome data were complete. Results for one subject were excluded to bad compliance with study regime.	--
	Detection Bias			
8.	Exposure characterisation	Yes	Mesoporous silica were precisely engineered and characterised for the study. There is indirect evidence that exposure may not have been consistently administered (with the same method and timeframe) across treatment groups.	+
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods (i.e. reporting of adverse events, clinical examinations). It is deemed lack of adequate blinding of outcome assessors would not appreciably bias results, as most outcome measures were objective (rather than subjective).	-
	Selective Reporting Bias			
10.	Outcome reporting	No	Indirect evidence that all of the study's measured outcomes have been reported.	-
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Jacqmin-Gadda et al. 1996

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cross-Sectional Studies greyed out.

Study ID: Jacqmin-Gadda et al. 1996 **Study Type: Cross-sectional (CrSe)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	

3.	Comparison groups appropriate	No	There is indirect evidence that subjects (both exposed and non-exposed) were similar (e.g. recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had the similar participation/response rates.	-
	Confounding bias			
4.	Confounding (design/analysis)	No	There is indirect evidence that appropriate adjustments were made and there is evidence (direct or indirect) that primary covariates and confounders were assessed using valid and reliable measurements.	-
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	**Blinding of researchers during study?**	**N/A**	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	Yes	NR: There is insufficient information provided about why subjects were removed from the study or excluded from analyses.	NR
	Detection Bias			
8.	Exposure characterisation	No	NR: There is insufficient information provided about the exposure assessment, including validity and reliability, but no evidence for concern about the method used.	-
9.	Outcome assessment	Yes	NR: There is insufficient information provided about blinding of outcome assessors.	NR
	Selective Reporting Bias			
10.	Outcome reporting	No	There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	-
	Other Sources of Bias			
11.	**Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)**	**N/A**		

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Jugdaohsingh et al. 2008

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Experimental Animal Studies greyed out.

Study ID: Jugdaohsingh et al. 2008	**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Study Type: Experimental Animal (EA)			
Q			

	Selection bias			
1.	Randomization	Yes	NR: there is insufficient information provided about how subjects were allocated to study groups.	NR
2.	Allocation concealment	Yes	There is indirect evidence that at the time of assigning study groups it was possible for the research personnel to know what group animals were allocated to, or it is likely that they could have broken the blinding of allocation before assignment was complete and irrevocable.	+
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	No	There is direct evidence that same vehicle was used in control and experimental animals, AND there is direct evidence that non-treatment-related experimental conditions were identical across study groups (i.e., the study report explicitly provides this level of detail).	--
6.	Blinding of researchers during study?	No	It is deemed that lack of adequate blinding during the study would not appreciably bias results, as it was not possible to undertake blinding due to requirement for feed and water renewal. Outcome measures were objective rather than subjective, so inadequate blinding is unlikely to appreciably bias results.	-
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is direct evidence that no loss of animals occurred in the study.	--
	Detection Bias			
8.	Exposure characterisation	No	There is indirect evidence that the exposure (including purity and stability of the test substance) was independently characterised and purity confirmed (i.e., the supplier of the chemical provides documentation of the purity of the chemical) AND there is indirect evidence that exposure was consistently administered (i.e., with the same method and time-frame) across treatment groups.	-
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods (i.e. deemed valid and reliable), AND assessed at the same length of time after initial exposure in all study groups, and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results, as results were objective outcome measures.	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Jugdaohsingh et al. 2015a

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Experimental Animal Studies greyed out.

Study ID: Jugdaohsingh et al. 2015a **Study Type: Experimental Animal (EA)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	Unknown	There is indirect evidence that animals were allocated to any study group including controls using a method with a random component (i.e. authors state that allocation was random, without description of the method used).	-
2.	Allocation concealment	Yes	There is indirect evidence that at the time of assigning study groups it was possible for the research personnel to know what group animals were allocated to, or it is likely that they could have broken the blinding of allocation before assignment was complete and irrevocable.	+
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	No	There is direct evidence that same vehicle was used in control and experimental animals, AND there is direct evidence that non-treatment-related experimental conditions were identical across study groups (i.e. the study report explicitly provides this level of detail).	--
6.	Blinding of researchers during study?	No	It is deemed that lack of adequate blinding during the study would not appreciably bias results, as it was not possible to undertake blinding due to requirement for feed and water renewal. Outcome measures were objective rather than subjective, so inadequate blinding is unlikely to appreciably bias results.	-
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is direct evidence that loss of animals was adequately addressed and reasons were documented when animals were removed from a study.	--
	Detection Bias			
8.	Exposure characterisation	No	There is indirect evidence that the exposure (including purity and stability of the test substance) was independently characterised and purity confirmed (i.e. the supplier of the chemical provides documentation of the purity of the chemical) AND there is indirect evidence that exposure was consistently administered (i.e. with the same method and time-frame) across treatment groups.	-
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods (i.e. deemed valid and reliable), AND assessed at the same length of time after initial exposure in all study groups, and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results, as results were objective outcome measures.	-
	Selective Reporting Bias			

10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Lewison et al. 1994

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Experimental Animal Studies greyed out.

Study ID: Lewison et al. 1994 **Study Type: Experimental Animal (EA)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	Yes	NR: There is insufficient information provided about how subjects were allocated to study groups.	NR
2.	Allocation concealment	Yes	NR: There is insufficient information provided about allocation to study groups.	NR
3.	Comparison groups appropriate	N/A	Comparison groups: not applicable	
	Confounding bias			
4.	Confounding (design/analysis)	N/A	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	No	There is direct evidence that same vehicle was used in control and experimental animals, AND there is direct evidence that non-treatment-related experimental conditions were identical across study groups (i.e. the study report explicitly provides this level of detail).	--
6.	Blinding of researchers during study?	Yes	NR: There is insufficient information provided about blinding to study group during the study.	NR
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is direct evidence that loss of animals was adequately addressed and reasons were documented when animals were removed from a study.	--
	Detection Bias			
8.	Exposure characterisation	No	There is indirect evidence that the exposure (including purity and stability of the test substance) was independently characterised and purity confirmed (i.e. the paper provides a table of physical properties of	-

			the two test substances) AND there is indirect evidence that exposure was consistently administered (i.e. with the same method and time-frame) across treatment groups.	
9.	Outcome assessment	Yes	NR: There is indirect evidence that it was possible for outcome assessors to infer the study group prior to reporting outcomes without sufficient quality control measures	NR
	Selective Reporting Bias			
10.	Outcome reporting	No	There is indirect evidence that all of the study's measured outcomes outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	-
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	Yes	Authors of paper are from test substance manufacturing organisation and there is no conflict of interest statement included in the paper.	++

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Liang et al. 2018

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Experimental Animal Studies greyed out.

Study ID: Liang et al. 2018 **Study Type: Experimental Animal (EA)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	Unknown	NR: There is insufficient information provided about how subjects were allocated to study groups	NR
2.	Allocation concealment	Unknown	NR: There is insufficient information provided about allocation to study groups	NR
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	No	There is direct evidence that the same vehicle was used in control and experimental animals and identical non-treatment-related experimental conditions are assumed as authors did not report differences in housing or husbandry.	-
6.	Blinding of researchers during study?	Unknown	NR: There is insufficient information provided about blinding to study groups during the study.	NR
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	No mortality was reported.	-

	Detection Bias			
8.	Exposure characterisation	Unknown	NR: There is insufficient information provided about the validity of the exposure assessment method (i.e. purity of substances used).	NR
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods (i.e. deemed valid and reliable but not the gold standard) and assessed at the same length of time after initial exposure in all study groups and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (more likely to apply to objective outcome measures).	-
	Selective Reporting Bias			
10.	Outcome reporting	No	Indirect evidence that all of the study's measured outcomes have been reported; selective reporting would not appreciably bias results.	-
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Markovic and Arambasic 1971

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Experimental Animal Studies greyed out.

Study ID: Markovic and Arambasic 1971 **Study Type: Experimental Animal (EA)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	Yes	NR: there is insufficient information provided about how subjects were allocated to study groups.	NR
2.	Allocation concealment	Yes	NR: there is insufficient information provided about allocation to study groups.	NR
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	No	There is direct evidence that same vehicle was used in control and experimental animals, AND identical non-treatment related experimental conditions are assumed as authors did not report differences in housing or husbandry.	-

6.	Blinding of researchers during study?	No	It is deemed that lack of adequate blinding during the study would not appreciably bias results, as it was not possible to undertake blinding due to requirement for feed and water renewal. Outcome measures were objective rather than subjective, so inadequate blinding is unlikely to appreciably bias results.	-
	Attrition/Exclusion Bias			
7.	Missing outcome data	Yes	NR: There is insufficient information provided about loss of animals.	NR
	Detection Bias			
8.	Exposure characterisation	Yes	NR: There is direct evidence that the exposure was assessed using indirect measures that have not been validated or empirically shown to be consistent with methods that directly measure exposure (i.e. in preparation of suspension, no verification of Si content appears to have been undertaken, guinea pigs may have been exposed to varying amounts of the suspension if they didn't drink a lot of it directly after mixing).	+
9.	Outcome assessment	Yes	NR: there is insufficient information provided about blinding of outcome assessors.	NR
	Selective Reporting Bias			
10.	Outcome reporting	Yes	There is indirect evidence that not all of the study's measured outcomes outlined in the protocol, methods, abstract and/or introduction (that are relevant for the evaluation) have been reported (e.g. incidence rates of nephrotoxicity are not provided).	+
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or Not Reported (NR)	+/NR	Definitely high risk of bias (++)	++

Mascarenhas et al. 2017

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cross-Sectional Studies greyed out.

Study ID: Mascarenhas et al. 2017 **Study Type: Cross-sectional (CrSe) / Observational**	**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q			
	Selection bias		
1.	**Randomization**	N/A	Randomization: not applicable	
2.	**Allocation concealment**	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is indirect evidence that subjects (both exposed and non-exposed) were similar (e.g. recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and	-

			exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had the similar participation/response rates.	
	Confounding bias			
4.	Confounding (design/analysis)	Yes	There is direct evidence that primary covariates and known confounders were not appropriately adjusted for in the final analyses.	++
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	**Blinding of researchers during study?**	**N/A**	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	Yes	NR: There is insufficient information provided about why subjects were removed from the study or excluded from analyses	NR
	Detection Bias			
8.	Exposure characterisation	No	Exposure (i.e. measurement of concentration in drinking water) was assessed using less-established methods that directly measure exposure and are validated against well-established methods.	--
9.	Outcome assessment	Yes	NR: There is insufficient information provided about blinding of outcome assessors.	NR
	Selective Reporting Bias			
10.	Outcome reporting	Yes	NR: There is insufficient information provided about selective outcome reporting.	NR
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	Yes	The study authors make a large claim in terms of silica exposure in groundwater (at 115.5 mg/L but not at ~13.5 mg/L) being the potential cause for CKD observed in some villages in India. However, no statistical analysis or odds ratios were calculated in this study and no correction for confounders was undertaken. The authors used the results of *in vitro* cytotoxicity assays to argue for such an association.	++

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Newberne and Wilson 1970

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Experimental Animal Studies greyed out.

Study ID: Newberne and Wilson 1970 **Study Type: Experimental Animal (EA)**	**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q			

	Selection bias			
1.	Randomization	Yes	NR: There is insufficient information provided about how subjects were allocated to study groups	NR
2.	Allocation concealment	Yes	NR: There is insufficient information provided about allocation to study groups.	NR
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	No	There is direct evidence that same vehicle was used in control and experimental animals, AND identical non-treatment-related experimental conditions are assumed as authors did not report differences in housing or husbandry.	-
6.	Blinding of researchers during study?	Yes	NR: There is insufficient information provided about blinding to study group during the study.	NR
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is direct evidence that there was no loss of animals throughout the study.	--
	Detection Bias			
8.	Exposure characterisation	Yes	NR: There is insufficient information provided about the validity of the exposure assessment method, but no evidence for concern.	NR
9.	Outcome assessment	Yes	NR: There is insufficient information provided about blinding of outcome assessors	NR
	Selective Reporting Bias			
10.	Outcome reporting	Yes	NR: There is insufficient information provided about selective outcome reporting	NR
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A		

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Rondeau et al. 2009

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cohort Studies greyed out.

Study ID: Rondeau et al. 2009 **Study Type: Cohort (Co)**	**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q			

	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is direct evidence that subjects (both exposed and non-exposed) were similar (e.g. recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had the similar participation/response rates.	--
	Confounding bias			
4.	Confounding (design/analysis)	No	There is direct evidence that appropriate adjustments or explicit considerations were made for primary covariates and confounders in the final analyses through the use of statistical models to reduce research-specific bias including standardization, matching, adjustment in multivariate model, stratification, propensity scoring, or other methods that were appropriately justified. AND there is direct evidence that primary covariates and confounders were assessed using valid and reliable measurements. AND there is direct evidence that other exposures anticipated to bias results were not present or were appropriately measured and adjusted for.	--
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	Missing data have been imputed using appropriate methods and characteristics of subjects lost to follow up or with unavailable records are described in identical way and are not significantly different from those of the study participants.	--
	Detection Bias			
8.	Exposure characterisation	No	Exposure was assessed using indirect measures (e.g. questionnaire) that have been validated or empirically shown to be consistent with methods that directly measure exposure (i.e. inter-methods validation: one method vs. another).	-
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using well-established methods and subjects had been followed for the same length of time in all study groups. Outcome measures were objectively assessed using diagnostic methods. There is indirect evidence that the outcome assessors were adequately blinded to the study group, as the exposures were not known to the medical practitioners undertaking the diagnoses.	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	Yes		

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Takizawa et al. 1988

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Experimental Animal Studies greyed out.

Study ID: Takizawa et al. 1988 **Study Type: Experimental Animal (EA)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	No	There is direct evidence that animals were allocated to any study group including controls using a method with a random component (i.e. standard randomisation), AND there is direct evidence that the study used a concurrent control group as an indication that randomisation covered all study groups.	--
2.	Allocation concealment	Yes	NR: There is insufficient information provided about allocation to study groups.	NR
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	No	There is direct evidence that same vehicle was used in control and experimental animals, AND there is direct evidence that non-treatment-related experimental conditions were identical across study groups (i.e., the study report explicitly provides this level of detail).	--
6.	Blinding of researchers during study?	Yes	NR: There is insufficient information provided about blinding to study group during the study.	NR
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is direct evidence that loss of animals was adequately addressed, and reasons were documented when animals were removed from a study. Missing outcome data balanced in numbers across study groups, with similar reasons for missing data across groups; missing outcomes are not enough to impact the effect estimate.	--
	Detection Bias			
8.	Exposure characterisation	Yes	NR: There is insufficient information provided about the validity of the exposure assessment method, but no evidence for concern.	NR
9.	Outcome assessment	Yes	NR: There is insufficient information provided about blinding of outcome assessors	NR
	Selective Reporting Bias			

10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported in sufficient detail to be included in meta-analysis or fully tabulated during data extraction.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A		

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Wolterbeek et al. 2015

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Experimental Animal Studies greyed out.

Study ID: Wolterbeek et al. 2015 **Study Type: Experimental Animal (EA)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	No	There is direct evidence that animals were allocated to any study group including controls using a method with a random component (computer randomisation on the basis of mean body weight) and there is direct evidence that the study used a concurrent control group as an indication that randomization covered all study groups. Pups were also selected at random.	--
2.	Allocation concealment	No	There is direct evidence that at the time of assigning study groups the research personnel did not know what group animals were allocated to, and it is unlikely that they could have broken the blinding of allocation until after assignment was complete and irrevocable. Acceptable methods used to ensure allocation concealment include sequentially numbered treatment containers of identical appearance or equivalent methods. The study states that males and females were placed with the same dosing group according to numerical sequence.	--
3.	Comparison groups appropriate	N/A	Comparison groups: not applicable	
	Confounding bias			
4.	Confounding (design/analysis)	N/A	Confounding: not applicable	
	Performance Bias			

5.	Identical experimental conditions	No	There is direct evidence that same vehicle was used in control and experimental animals, AND there is direct evidence that non-treatment-related experimental conditions were identical across study groups (i.e., the study report explicitly provides this level of detail).	--
6.	Blinding of researchers during study?	Yes	NR: There is insufficient information provided about blinding to study group during the study.	NR
	Attrition/Exclusion Bias			
7.	Missing outcome data	Yes	NR: There is insufficient information provided about loss of animals.	+
	Detection Bias			
8.	Exposure characterisation	Yes	There is direct evidence that the exposure (including purity and stability of the test substance) was independently characterised and purity confirmed (i.e. the paper provides purity as 96.5% SiO_2). Note this is <98% specified in OHAT protocol to represent the difference between 'probably low' and 'probably high' risk of bias. There is direct evidence that exposure was consistently administered (i.e. with the same method and time-frame) across treatment groups. Due to <98% purity, this has been allocated to 'probably high' risk of bias.	+
9.	Outcome assessment	No	There is direct evidence that the outcome was assessed using well-established methods (the gold standard) AND assessed at the same length of time after initial exposure in all study groups. It is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results, as results were objective measures and no adverse effects were found in any study group.	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported and reported to sufficient detail.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A		

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Yoo et al. 2022

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Experimental Animal Studies greyed out.

Study ID: Yoo et al. 2022	**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Study Type: Experimental Animal (EA)			
Q			

	Selection bias			
1.	Randomization	Yes	NR: There is insufficient information provided about how subjects were allocated to study groups	NR
2.	Allocation concealment	Yes	NR: There is insufficient information provided about allocation to study groups.	NR
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	No	There is direct evidence that same vehicle was used in control and experimental animals, AND there is direct evidence that non-treatment-related experimental conditions were identical across study groups (i.e. the study report explicitly provides this level of detail).	--
6.	Blinding of researchers during study?	Yes	NR: There is insufficient information provided about blinding to study group during the study.	NR
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is direct evidence that there was no loss of animals throughout the study.	--
	Detection Bias			
8.	Exposure characterisation	Yes	NR: There is insufficient information provided about the validity of the exposure assessment method, but no evidence for concern.	NR
9.	Outcome assessment	No	There is direct evidence that the outcome was assessed using well-established methods (the gold standard) AND assessed at the same length of time after initial exposure in all study groups. It is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results, as results were objective measures and no adverse effects were found in either study group.	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported and reported to sufficient detail.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A		

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

APPENDIX E

Data extraction tables – Supporting Information for Factsheet

Supporting Information for Silicon Factsheet

EFSA 2004

Reference: EFSA (2004). Opinion of the Scientific Panel on Dietetic products, nutrition and allergies [NDA] related to the Tolerable Upper Intake Level of Silicon. EFSA Journal 2(5): 60.		
General Description	Uses	-
	Sources in drinking water	-
	Other	• One study referenced in the review indicates concentrations of Si in drinking water in the UK were all <6 mg/L (Dobbie and Smith 1986). • Silicon is a non-metallic element with atomic weight of 28. It occurs in the earth's crust at an average concentration of about 28%, but does not exist in nature in forms other than as silicon dioxide (silica) or as silicates (Friedberg and Schiller, 1988). Silica consists of free silicon dioxide, which is amorphous (e.g. diatomaceous earth) or crystalline (e.g. quartz, tridymite and cristobalite), or in combination with various cations as silicates (e.g. Fuller's earth, asbestos, talc and mica). Silicon in water is present as orthosilicic acid $Si(OH)_4$. Silicic acid exists as monosilicic acid. A saturated solution contains 0.1% silicic acid. Silicic acid can also exist as oligomers and as polysilicic acid, which is colloidal. The chemistry of silicon has many similarities to that of carbon. It forms bonds with silicon, hydrogen, oxygen, nitrogen and carbon. The substitution of carbon for silicon in organic compounds results in molecules with different properties due to a larger size and electronegativity of silicon.
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	Si addition to drinking water containing Al reduces the plasma peak of Al in humans.
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	-
	Other	-
Additional information	Any additional non-health related information considered important?	-

EFSA 2009

Reference: EFSA (2009). Calcium silicate and silicon dioxide/silicic acid gel added for nutritional purposes to food supplements. EFSA Journal 7(6): 1132.		
General Description	Uses	Silicon occurs naturally in foods as silicon dioxide (SiO_2, silica) and silicates. High levels of silicon are found in foods derived from plants, and particularly cereals, whereas silicon levels are lower in foods from animal sources.
	Sources in drinking water	-
	Other	Orthosilicic acid [$Si(OH)_4$] is the major silicon species present in drinking water and other liquids, including beer, and is the most readily available source of silicon to man. After oral consumption, the main chemical species by which silicon is absorbed is orthosilicic acid.
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	-
	Other	-
Additional information	Any additional non-health related information considered important?	-

EFSA 2010

Reference: EFSA (2010). Selected trace and ultratrace elements: Biological role, content in feed and requirements in animal nutrition – Elements for risk assessment. EFSA Supporting Publications, European Food Safety Authority. 7**:** 68E.		
General Description	Uses	Silicon occurs naturally in foods as silicon dioxide (silica) and silicates. Orthosilicic acid ($Si(OH)_4$) is the major silicon species present in drinking water and other liquids e.g., beer (EFSA, 2004). Several silicon compounds are allowed as food and feed additives as anti-caking and anti-foaming agents.
	Sources in drinking water	-
	Other	-
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-

Reference: EFSA (2010). Selected trace and ultratrace elements: Biological role, content in feed and requirements in animal nutrition – Elements for risk assessment. EFSA Supporting Publications, European Food Safety Authority. 7**:** 68E.		
	Limit of determination/ Limit of Reporting (LOR)	-
	Other	-
Additional information	Any additional non-health related information considered important?	-

EFSA 2018a

Reference: EFSA (2018a). Safety of orthosilicic acid-vanillin complex (OSA-VC) as a novel food ingredient to be used in food supplements as a source of silicon and bioavailability of silicon from the source. EFSA Journal 16(1): e05086.		
General Description	Uses	Silicon is an ubiquitous element present in the environment. It is mainly found as insoluble silicates, but small amounts of soluble silicon are naturally present in water, chiefly as orthosilicic acid, $Si(OH)_4$ which is the most bioavailable source of silicon. Silicon dioxide, calcium, magnesium and potassium silicates (E 551–553) are authorised food additives in the European Union (EU).
	Sources in drinking water	-
	Other	Average dietary intake of Si (excluding supplements) is 20–50 mg/day (EFSA 2004).
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	-
	Other	-
Additional information	Any additional non-health related information considered important?	-

EFSA 2018c

Reference: EFSA (2018c). Re-evaluation of calcium silicate (E 552), magnesium silicate (E 553a(i)), magnesium trisilicate (E 553a(ii)) and talc (E 553b) as food additives. EFSA Journal 16(8): e05375.		
General Description	Uses	Calcium silicate (E 552), magnesium silicate (E 553a) and talc (E553b) are authorised as food additives in the EU. Calcium silicate, magnesium silicate, magnesium trisilicate and talc are permitted as ingredients in cosmetic products. Calcium silicate is included in the European Union Register of feed additives.
	Sources in drinking water	-
	Other	-
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	-
	Other	-
Additional information	Any additional non-health related information considered important?	-

EVM 2003

Reference: EVM (2003). Safe upper limits for vitamins & minerals, Expert Group on Vitamins and Mineral.		
General Description	Uses	Silicon (Si) is a non-metallic element with an atomic weight of 28. The term 'silica' is used to refer to naturally occurring materials composed principally of silicon dioxide (SiO_2), whereas 'silicone' (organosiloxane) refers to man-made siloxane polymers based on a structure of alternating oxygen and silicon atoms. Silicon is not found freely in nature but occurs chiefly as the oxide and silicates. Silica (SiO_2) occurs in nature in several different forms: crystalline (quartz, cristobalite and tridymite) and amorphous. When exposed to water, silicates liberate orthosilicic acid to a concentration of 1-15 mg/L. High levels of silicon are found in foods derived from plants, particularly grains such as oats (4250 mg/kg wet weight), barley (2420 mg/kg wet weight) or rice. Levels are lower in foods from animal sources. Beer is also a rich source of silica containing 33-60 mg/kg. Silicon is also found in drinking water as orthosilicic acid. Amorphous silica is used as a food additive, in particular as an anti-caking agent, but also to clarify beverages, control viscosity and as an anti-foaming agent and dough modifier. It is also used as an anti-caking agent and as an excipient in pharmaceuticals for various drug and vitamin preparations. UK food supplements contain up to 500 mg silicon.

Reference: EVM (2003). Safe upper limits for vitamins & minerals, Expert Group on Vitamins and Mineral.		
	Sources in drinking water	-
	Other	Exposures: • Food: Up to 50 mg/day. • Supplements: Up to 500 mg/day • Water: 10 mg/day (assuming 2 L of water at 5 mg/L) Estimated maximum total intake = 560 mg/day
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	-
	Other	-
Additional information	Any additional non-health related information considered important?	-

FAO/WHO 1969

Reference: FAO and WHO (1969). Toxicological evaluation of some food colours, emulsifiers, stabilizers, anti-caking agents and certain other substances, Food Agriculture Organization of the United Nations and World Health Organization.		
General Description	Uses	-
	Sources in drinking water	-
	Other	-
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	-
	Other	-
Additional information	Any additional non-health related information considered important?	-

FAO/WHO 1974

Reference: FAO and WHO (1974). Silicon Dioxide and Certain Silicates, Food Agriculture Organization of the United Nations and World Health Organization.		
General Description	Uses	Silica, silicic acid and the calcium, magnesium and aluminium salts occur ubiquitously in the environment and some have been used for many years medically. Food contains various amount of SiO_2, for example: potatoes 10.1, milk 2.1, drinking water 7.1, mineral water 22.5, beer 131 gammaSiO_2 per g or cm^3.
	Sources in drinking water	-
	Other	-
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	-
	Other	-
Additional information	Any additional non-health related information considered important?	-

Benson et al. 2017

Reference: Benson R., Conerly O. D., Sander W., Batt A. L., Boone J. S., Furlong E. T., Glassmeyer S. T., Kolpin D. W., Mash H. E., Schenck K. M. and Simmons J. E. (2017). Human health screening and public health significance of contaminants of emerging concern detected in public water supplies. Sci Total Environ 579: 1643-1648.		
General Description	Uses	-
	Sources in drinking water	-
	Other	This paper describes a study in which source water and treated drinking water from 25 drinking water treatment plants (DWTP) across the USA were sampled in 2010-2012; samples were analysed for 247 analytes using 15 chemical and microbiological methods (silicon was included). Silicon was detected in the treated water from every DWTP. The maximum concentration detected was 22.26 mg/L.
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-

Reference: Benson R., Conerly O. D., Sander W., Batt A. L., Boone J. S., Furlong E. T., Glassmeyer S. T., Kolpin D. W., Mash H. E., Schenck K. M. and Simmons J. E. (2017). Human health screening and public health significance of contaminants of emerging concern detected in public water supplies. Sci Total Environ 579: 1643-1648.		
Measurement	Analytical method	Not specifically stated in paper. May be included in 'United States Environmental Protection Agency (USEPA) metals, anions, perchlorate and Total Organic Carbon (TOC)' method. Analytical methods listed for this are Inductively Coupled/Mass Spectrometry (IC/MS, IC/Absorption Emission Spectrometry (AES), titration and LC/MS/MS.
	Limit of determination/ Limit of Reporting (LOR)	Not specifically stated in this publication for silicon.
	Other	-
Additional information	Any additional non-health related information considered important?	Authors used a NOAEL of 800 mg/kg bw/d (source not provided) and a target margin of exposure (MOE) of 3,000 to judge the importance of the maximum Si concentration obtained in drinking water. The calculated MOE was 1,200 for one DWTP. Authors state: "*As there is uncertainty in the selected screening MOE due to the poor quality of the toxicity data base for silicon, it would be helpful if additional toxicity data were collected*."

Choucri et al. 2021

Reference: Choucri J., Balbo A., Zanotto F., Grassi V., Touhami M. E., Mansouri I. and Monticelli C. (2021). Corrosion Behavior and Susceptibility to Stress Corrosion Cracking of Leaded and Lead-Free Brasses in Simulated Drinking Water. Materials (Basel) 15(1).		
General Description	Uses	Silicon brasses with various compositions were developed to induce grain refining and strength increase or to produce non-toxic Pb- and As-free alloys with good machinability and dezincification resistance. CuZn21Si3P is a dezincification resistant brass with α + κ microstructure, where κ is a hard Si-rich phase. Its resistance to selective Zn leaching is ensured by the "phosphorus cycle" adopted as an alternative to the analogous "arsenic cycle". Actually, in this alloy a significant dealloying process cannot be avoided during long immersions (150 days) in simulated drinking water (SDW).
	Sources in drinking water	-

Reference: Choucri J., Balbo A., Zanotto F., Grassi V., Touhami M. E., Mansouri I. and Monticelli C. (2021). Corrosion Behavior and Susceptibility to Stress Corrosion Cracking of Leaded and Lead-Free Brasses in Simulated Drinking Water. Materials (Basel) 15(1).		
	Other	In this study, the corrosion behaviour and stress corrosion cracking (SCC) susceptibility of two leaded (CW617N and CW602N) alloys and one lead-free silicon brass (CW724R) were investigated in SDW solutions containing different chloride concentrations. The alloys suffered from spot dealloying that is preferential zinc (alloys CW61N and CW602N) and zinc and silicon (ally CW724R) dissolution already after 24 h immersion. The SSRT evidenced that all brass types and particularly CW617N exhibited susceptibility to SCC. During the tests, CW602N and CW724R exhibited discontinuous mechanical slips more frequent in SDW solutions than in air, likely due to the onset of dealloying-induced additive tensile stresses.
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	-
	Other	-
Additional information	Any additional non-health related information considered important?	-

Desai et al. 2012

Reference: Desai J. S. (2012). Studies on some physico-chemical and microbiological characteristic of potable water used in some different area of Ahmedabad in Gujarat. 3: 1006-1014.		
General Description	Uses	-
	Sources in drinking water	-
	Other	Water samples collected in first week of Jan 2005 and first week of April 2005 in different areas of Ahmedabad, India and analysed for Si amongst other analytes. Concentrations ranged from 18.2 – 53.9 mg/L
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-

Reference: Desai J. S. (2012). Studies on some physico-chemical and microbiological characteristic of potable water used in some different area of Ahmedabad in Gujarat. 3: 1006-1014.		
Measurement	Analytical method	Spectrophotometric analysis using 'Hach-odyssey spectrophotometer'
	Limit of determination/ Limit of Reporting (LOR)	Not reported
	Other	-
Additional information	Any additional non-health related information considered important?	-

Fujita et al. 2014

Reference: Fujita M., Ishiwatari Y., Mishima I., Utsuno N. and Kato T. (2014). Effect of Ageing of Pipe and Lining Materials on Elemental Composition of Suspended Particles in a Water Distribution System. Water Resources Management 28.		
General Description	Uses	-
	Sources in drinking water	-
	Other	This study involved collection of water samples from 10 sampling sites in a drinking water supply system in Japan and assessing suspended particles for their elemental composition, including silicon. While each elemental concentration varied according to sampling site, Si and Fe commonly accounted for 70-95% of the total concentration. Si concentrations were not significantly correlated with other elements.
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	ICP-AES and ICP-MS (for suspended material)
	Limit of determination/ Limit of Reporting (LOR)	-
	Other	-
Additional information	Any additional non-health related information considered important?	-

Ghaffari et al. 2021

Reference: Ghaffari H. R., Kamari Z., Ranaei V., Pilevar Z., Akbari M., Moridi M., Khedher K. M., Thai V. N., Fakhri Y. and Mousavi Khaneghah A. (2021). The concentration of potentially hazardous elements (PHEs) in drinking water and non-carcinogenic risk assessment: A case study in Bandar Abbas, Iran. Environ Res 201: 111567.		
General Description	Uses	-
	Sources in drinking water	-
	Other	This study involved measuring concentrations of various elements (including silicon) in tap drinking water (n=40) and filtration plants (n=22) in Bandar Abbas city between March and July 2020. The study found mean ± SD concentration of Si in tap water was 6,356.25 ± 1282 µg/L (i.e. 6.3 mg/L) with concentrations in the filtration plant at 1825 ± 748 µg/L (i.e. 1.8 mg/L). The mean concentrations were found to be significantly different between tap water and water from the filtration plant.
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	ICP-MS
	Limit of determination/ Limit of Reporting (LOR)	10 µg/L
	Other	-
Additional information	Any additional non-health related information considered important?	-

Ikehata et al. 2018

Reference: Ikehata K., Zhao Y., Kulkarni H. V., Li Y., Snyder S. A., Ishida K. P. and Anderson M. A. (2018). Water Recovery from Advanced Water Purification Facility Reverse Osmosis Concentrate by Photobiological Treatment Followed by Secondary Reverse Osmosis. Environ Sci Technol 52(15): 8588-8595.		
General Description	Uses	-
	Sources in drinking water	-
	Other	Thus study explored the feasibility of additional water recovery from advanced water purification facility (AWPF) reverse osmosis (RO) concentrate by photobiological treatment followed by secondary RO.
Treatment of drinking water	Treatment technology	A new diatom-based photobiological process has been developed to remove scaling constituents by biological uptake and precipitation. In this study, RO concentrate samples were collected from a full-scale advanced water reclamation facility in California and were treated in 3.8 and 57 L photobioreactors inoculated with a brackish water diatom *Pseudostaurosira trainorii* PEWL001 using light-emitting diode bulbs or natural sunlight as a light source.

Reference: Ikehata K., Zhao Y., Kulkarni H. V., Li Y., Snyder S. A., Ishida K. P. and Anderson M. A. (2018). Water Recovery from Advanced Water Purification Facility Reverse Osmosis Concentrate by Photobiological Treatment Followed by Secondary Reverse Osmosis. Environ Sci Technol 52(15): 8588-8595.		
	Effectiveness	The photobiological treatment removed 95% of reactive silica and enabled additional water recovery using a secondary RO at a recovery rate up to 66%.
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	-
	Other	-
Additional information	Any additional non-health related information considered important?	-

Morykwas et al. 1991

Reference: Morykwas M. J., Rouchard R. A. and Argenta L. C. (1991). Silicon levels in treated drinking water. Plast Reconstr Surg 88(5): 925-926.		
General Description	Uses	-
	Sources in drinking water	The majority of silicon in treated waters in USA is in the form of SiO_2, although a great variety of compounds of silicon are present.
	Other	To determine possible sources of silicon found in humans, authors contacted water purification facilities throughout USA and compared levels of silicon compounds from a variety of sites located around the country. Concentrations of Si cited for a number of different cities in USA range from 0.32 to 33 mg/L, with means ranging from 0.68 to 17.3 mg/L.
Treatment of drinking water	Treatment technology	-
	Effectiveness	
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	-
	Other	-
Additional information	Any additional non-health related information considered important?	-

NRC 1979

Reference: NRC (1979). The contribution of drinking water to mineral nutrition in humans, Original from: Gov. Rep. Announce. Index (U. S.) 1980, 80(4), 478.		
General Description	Uses	-
	Sources in drinking water	-
	Other	The maximum, median, and minimum concentrations of silicon as silica in finished water from water supplies of the 100 largest cities of the USA were 72, 7.1 and 0 mg/L; no mean concentrations were given. Natural waters may contain from a few to several thousand mg Si/L (location not specified). Increased urinary Si output with increasing intake up to fairly well-defined limits has been demonstrated in humans, rats and guinea pigs. The rate of excretion does not seem to be dependent on the renal capabilities to excrete silicon but rather, on the extent of silicon absorption.
Treatment of drinking water	Treatment technology	-
	Effectiveness	
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	-
	Other	-
Additional information	Any additional non-health related information considered important?	-

Powell et al. 2005

Reference: Powell J. J., McNaughton S. A., Jugdaohsingh R., Anderson S. H., Dear J., Khot F., Mowatt L., Gleason K. L., Sykes M., Thompson R. P., Bolton-Smith C. and Hodson M. J. (2005). A provisional database for the silicon content of foods in the United Kingdom. Br J Nutr 94(5): 804-812.		
General Description	Uses	-
	Sources in drinking water	-

Reference: Powell J. J., McNaughton S. A., Jugdaohsingh R., Anderson S. H., Dear J., Khot F., Mowatt L., Gleason K. L., Sykes M., Thompson R. P., Bolton-Smith C. and Hodson M. J. (2005). A provisional database for the silicon content of foods in the United Kingdom. Br J Nutr 94(5): 804-812.		
	Other	A total of 207 foods and beverages, commonly consumed in the UK, were analysed for Si content. Composite samples were analysed using ICP–optical emission spectrometry following micro-wave-assisted digestion with nitric acid and H_2O_2. The highest concentrations of Si were found in cereals and cereal products, especially less refined cereals and oat-based products. Fruit and vegetables were highly variable sources of Si with substantial amounts present in Kenyan beans, French beans, runner beans, spinach, dried fruit, bananas and red lentils, but undetectable amounts in tomatoes, oranges and onions. Of the beverages, beer, a macerated whole-grain cereal product, contained the greatest level of Si, whilst drinking water was a variable source with some mineral waters relatively high in Si. Tap water (n=4) contained a mean of 0.25 ± 0.11 mg/100g (i.e. ~2.5 mg/L).
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	ICP–optical emission spectrometry
	Limit of determination/ Limit of Reporting (LOR)	-
	Other	-
Additional information	Any additional non-health related information considered important?	-

Prescha et al. 2012

Reference: Prescha A., Zabłocka-Słowińska K., Hojka A. and Grajeta H. (2012). Instant food products as a source of silicon. Food Chem 135(3): 1756-1761.		
General Description	Uses	Used in instant food products.
	Sources in drinking water	-
	Other	Silicon content measured in instant food products as well as in the drinking water used for preparation of some food products. Drinking water from Wroclaw (Poland) and its vicinity (n=6, sampled five times at monthly intervals) contained an average of 7.09 mg Si/L (range of means = 2.92 – 13.41 mg/L).
Treatment of drinking water	Treatment technology	-
	Effectiveness	-

Reference: Prescha A., Zabłocka-Słowińska K., Hojka A. and Grajeta H. (2012). Instant food products as a source of silicon. Food Chem 135(3): 1756-1761.		
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	-
	Other	-
Additional information	Any additional non-health related information considered important?	-

Rauf et al. 2021

Reference: Rauf A. U., Mallongi A., Daud A., Hatta M. and Astuti R. D. P. (2021). Ecological risk assessment of hexavalent chromium and silicon dioxide in well water in Maros Regency, Indonesia. Gac Sanit 35 Suppl 1: S4-s8.		
General Description	Uses	-
	Sources in drinking water	-
	Other	This paper reports the concentrations of SiO_2 in 14 well water samples collected around the residential area near cement industrial activity and karst mining in Indonesia. Mean SiO_2 concentration was 12.94 mg/L (range 7.4 – 20.9 mg/L). It is noted this paper also calculated hazard quotients for SiO_2 exposure, apparently using "*data of MRL of silicon dioxide through oral from male rat experiments is 2.030 mg/day*". The authors cite a 2019 Agency for Toxicological Substances and Disease Registry (ATSDR) toxicological profile for silica. Upon consultation of the profile, no oral Minimal Risk Level (MRL) was derived for silica. In addition the units of an MRL are typically expressed as a dose. It is therefore unclear what data for SiO_2 Rauf et al. (2021) used to calculate their hazard quotients, and whether the resulting Hazard Quotients (HQs) are reliable. The risk assessment conclusions in the paper should therefore not be relied upon.
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	-
	Other	-

Reference: Rauf A. U., Mallongi A., Daud A., Hatta M. and Astuti R. D. P. (2021). Ecological risk assessment of hexavalent chromium and silicon dioxide in well water in Maros Regency, Indonesia. Gac Sanit 35 Suppl 1: S4-s8.		
Additional information	Any additional non-health related information considered important?	-

Rawat et al. 2020

Reference: Rawat K., Singh, S. K., Tripathi, V.K. (2020). Assessment of silica content in groundwater of Peninsular Indian region using statistical techniques. **Ind J of Geo**, v. 52, n. 3, p. 374-386, dec. 2020. ISSN 2354-9114		
General Description	Uses	-
	Sources in drinking water	Groundwater from open dug wells in Chennai, India.
	Other	This study assessed silica in groundwater (n=12 wells) to establish baseline concentrations. Silica was present at 15.5 – 24 mg/L according to the data collected from the Central Groundwater Board-Chennai. Method of measurement not reported.
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	-
	Other	-
Additional information	Any additional non-health related information considered important?	-

Selianova et al. 2010

Reference: Selivanova T. V., Vishnikin A. B. and Tsyganok L. P. (2010). Sorption—spectrophotometric and visual test determination of trace silicon as an ion associate of 12-molybdosilicate with crystal violet. Journal of Analytical Chemistry 65(2): 142-147.		
General Description	Uses	-
	Sources in drinking water	-
	Other	-
Treatment of drinking water	Treatment technology	-
	Effectiveness	-

Reference: Selivanova T. V., Vishnikin A. B. and Tsyganok L. P. (2010). Sorption—spectrophotometric and visual test determination of trace silicon as an ion associate of 12-molybdosilicate with crystal violet. Journal of Analytical Chemistry 65(2): 142-147.		
	Any special conditions?	-
	Other	-
Measurement	Analytical method	Describes new method: Highly sensitive procedure for spectrophotometric determination of silicon by the adsorption of an ion associate of 12-molybdosilicate with crystal violet (MSC) on polyurethane foams (PUF).
	Limit of determination/ Limit of Reporting (LOR)	3-6 µg/L
	Other	-
Additional information	Any additional non-health related information considered important?	-

Vertrimurugan et al. 2017

Reference: Vetrimurugan E., Brindha K., Elango L. and Ndwandwe O. M. (2017). Human exposure risk to heavy metals through groundwater used for drinking in an intensively irrigated river delta. Applied Water Science 7(6): 3267-3280.		
General Description	Uses	-
	Sources in drinking water	-
	Other	This study sampled groundwater (n=40) in an intensively irrigated part of the Cauvery river basin, Tamil Nadu, India in January 2015 and determined suitability for drinking use based on analysing for a suite of metals/elements. The concentration of Si ranged from <LOR (LOR not reported) to 26.48 mg/L (mean = 9.82 mg/L).
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	Inductively coupled plasma mass spectrometry
	Limit of determination/ Limit of Reporting (LOR)	Not provided.
	Other	-
Additional information	Any additional non-health related information considered important?	-

Melbourne Water 2021

Reference: Melbourne Water (2021). Testing water quality- Monthly Report, June 2021, Melbourne Water.		
General Information	Date of data extraction	29/05/2023
	Authors	Not listed.
	Publication date	2021
	Publication type	Drinking Water Corporation report.
	Description	No guidance value derived in this document *per se* but contains relevant information on Si exposure levels in Australian drinking water supply system (may or may not be relevant for context).
	Findings	• Cardinia: 3.9-5.7 mg/L • Greenvale: 2.3-7.2 mg/L • Silvan: 5.9-7.0 mg/L • Winneke: 3.4-5.3 mg/L

PWNT 2020

Reference: PWNT (2020). Annual Drinking Water Quality Report 2020. Power and Water Corporation Northern Territory.		
General Information	Date of data extraction	29/05/2023
	Authors	Not listed.
	Publication date	2020
	Publication type	Drinking Water Corporation report.
	Description	No guidance value derived in this document *per se* but contains relevant information on Si exposure levels in Australian drinking water supply system (may or may not be relevant for context).

Reference: PWNT (2020). Annual Drinking Water Quality Report 2020. Power and Water Corporation Northern Territory.		
	Findings	Mean values in major centres (as SiO_2): • Alice Springs (n=8): 17 mg/L • Darwin (n=18): 11 mg/L • Katherine (n=4): 15 mg/L • Tennant Creek (n=8): 86 mg/L • Yulara (n=8): 15 mg/L • Adelaide River (n=6): 27 mg/L • Batchelor (n=6): 18 mg/L • Borroloola (n=6): 14 mg/L • Garawa (n=4): 14 mg/L • Cox Peninsula (n=4): 21 mg/L • Daly Waters (n=8): 33 mg/L • Elliott (n=6): 48 mg/L • Gunn Point (n=4): 10 mg/L • Kings Canyon (n=4): 20 mg/L • Larrimah (n=4): 41 mg/L • Mataranka (n=4): 29 mg/L • Newcastle Water (n=6): 55 mg/L • Pine Creek (n=6): 50 mg/L • Ti Tree (n=37): 91 mg/L • Timber Creek (n=12): 22 mg/L In regional communities, mean values were similar ranging from 11 to 104 mg/L.

WCWA 2020

Reference: WCWA (2020). Drinking Water Quality Annual Report 2019-20. Water Corporation, Western Australia		
General Information	Date of data extraction	29/05/2023
	Authors	Not listed.
	Publication date	2020
	Publication type	Drinking Water Corporation report.
	Description	No guidance value derived in this document *per se* but contains relevant information on Si exposure levels in Australian drinking water supply system (may or may not be relevant for context).

Reference: WCWA (2020). Drinking Water Quality Annual Report 2019-20. Water Corporation, Western Australia		
	Findings	Mean values (range) for example areas: • Armadale/Kelmscott: 2.6 (1.9-3.2) mg/L • Bold Park: 3.1 (1.8-4.4) mg/L • Buckland Hill: 6.8 (5.4-8.1) mg/L • Dwellingup: 2.1 (1.9-2.2) mg/L • Foothills: 3.9 (3.7-4.0) mg/L • Greenmount: 17.3 (16-18) mg/L • Greenmount/Darlington: 7.3 (6.1-9.8) mg/L • Hamilton Hill: 5.3 (5.1-5.4) mg/L • Hills Direct: 1.6 (1.3-1.9) mg/L • Lexia: 16 (12-20) mg/L • Mandurah: 1 (0.8-1.3) mg/L • Melville: 4.8 (4-5.2) mg/L • Mirrabooka: 14.5 (14-15 mg/L) • Mt Eliza: 6.5 (4.9-8.6) mg/L • Mt Hawthorn: 14.8 (13-17) mg/L • Mt Yokine: 17 (16-18) mg/L • Mundaring: 4.9 (4.4-5.4) mg/L • Neerabup: 19.8 (19-21) mg/L • North Dandalup: 1.8 (1.6-2.2) mg/L • Pinjarra: 2 (1.9-2) mg/L • South Perth/Kewdale: 15.5 (14-17) mg/L • Tamworth Hill: 0.9 (0.7-1.2) mg/L • Thomsons Lake: 5.5 (4.6-5.9) mg/L • Two Rocks: 11.6 (11-12) mg/L • Wanneroo: 18.5 (17-21) mg/L • West Yokine: 17 (16-18) mg/L • Whitfords: 16 (15-17) mg/L • Yanchep: 16 (15-17) mg/L Ranges in other areas of WA: • Range of means: 0.6 to 90 mg/L

APPENDIX F

Existing guideline/guidance assessment tables

Criteria for assessing existing guidance or guidelines

Administrative and technical criteria for assessing existing guidance or guidelines

Criteria have been colour-coded to assess minimum requirements as follows: 'Must have', 'Should have' or 'May have'

EVM 2003

Agency Report Reference: EVM (2003). Safe Upper Levels for Vitamins and Minerals. UK Expert Group on Vitamins and Minerals. May 2003.

Criteria		Y/N/?/NA	Notes
	Overall guidance/advice development process		
	Are the key stages of the organisation's advice development processes compatible with Australian processes?	Y	Yes, as indicated in the introductory chapters of the document.
	Are the administrative processes documented and publicly available?	Y	Yes, documented in the introductory chapters of the document.

Criteria		Y/N/?/NA	Notes
	Was the work overseen by an expert advisory committee? Are potential conflicts of interest of committee members declared, managed and/or reported?	Y	Yes. EVM Members were drawn from the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), the Committee on Safety of Medicines (CSM), the Committee on the Medical Aspects of Food and Nutrition Policy (COMA) and the Food Advisory Committee (FAC). The membership represented a range of expertise in toxicology, pharmacology, epidemiology, medicine and nutrition as well as a non-specialist Member to represent consumer interests. Two further EVM Members with nutritional and toxicological expertise were also nominated by the main interest groups. Observers were also appointed to act as a link between EVM and its main stakeholders; the observers were able to contribute to discussions of general issues, but did not contribute to the risk assessment process. Members and, where applicable, observers agreed to abide by the Code of Practice (document EVM/99/11) which covers matters dealing with conflicts of interest. Members were required to declare any interests prior to the discussion of the item concerned. Where a direct, personal interest was apparent, the Member concerned was not permitted to contribute to the risk assessment process. This was recorded in the minutes of the meeting. The observers were not required to declare interests since they were presumed to be representing interest groups. They were therefore unable to contribute to the risk assessment process.
	Are funding sources declared?	N (1/2)	Not stated, but presumably UK government.
	Was there public consultation on this work? If so, provide details.	Y	Yes, as detailed in Chapter 7 of the report.
	Is the advice peer reviewed? If so, is the peer review outcome documented and/or published?	Y	Considered peer reviewed, as it was a collation of advice by numerous members of the Expert Group. In addition, public consultation resulted in peer review by other academics/scientists as well as the general public and medical practitioners.
	Was the guidance/advice developed or updated recently? Provide details.	N	No updates to this document have been located.
	Evidence review parameters		
	Are decisions about scope, definitions and evidence review parameters documented and publicly available?	Y	Yes, as indicated in the introductory chapters of the document.

Criteria		Y/N/?/NA	Notes
	Is there a preference for data from studies that follow agreed international protocols or meet appropriate industry standards?	Y	Yes, the report specifies that good quality data should be given more weight than poor quality data. It provides information for each study type considered and what study types were included/excluded for review of the evidence.
	Does the organisation use or undertake systematic literature review methods to identify and select data underpinning the advice? Are the methods used documented clearly?	?	Not specified. The details of the literature search approach (apart from the cutoff date and type of studies included/excluded) was not specified explicitly in the document.
	If proprietary/confidential studies or data are considered by the agency, are these appropriately described/recorded?	Y	Yes, although this appears to have been limited to exposure information for drug usage.
	Are inclusion/exclusion criteria used to select or exclude certain studies from the review? If so, is justification provided?	Y	Yes, this is summarised in the introductory sections of the report.
	Does the organisation use or adopt review findings or risk assessments from other organisations? What process was used to critically assess these external findings?	NA	
	Can grey literature such as government reports and policy documents be included?	Y	Yes, grey literature appears to have been included in certain instances, especially for the exposure information summaries.
	Is there documentation and justification on the selection of a toxicological endpoint for use as point of departure for health-based guideline derivation?	Y	Yes, each nutrient/vitamin considered in the report provides detailed derivation for what is considered the point of departure and why.
	Evidence search		
	Are databases and other sources of evidence specified?	Y (1/2)	Search details not provided, but all references cited listed in bibliography.
	Does the literature search cover at least more than one scientific database as well as additional sources (which may include government reports and grey literature)?	?	Unknown. Search details not provided.
	Is it specified what date range the literature search covers? Is there a justification?	Y	Yes. Cutoff date for literature search specified as September 2001.
	Are search terms and/or search strings specified?	N	No. Search details not provided.
	Are there any other exclusion criteria for literature (e.g. publication language, publication dates)? If so, what are they and are they appropriate?	?	Unknown. Search details not provided.
	Critical appraisal methods and tools		

Criteria		Y/N/?/NA	Notes
	Is risk of bias of individual studies taken into consideration to assess internal validity? If so, what tools are used? If not, was any method used to assess study quality?	N	Although the report provides information regarding what types of studies were considered to be of highest quality, the evaluation does not appear to have taken a traditional systematic approach.
	Does the organisation use a systematic or some other methodological approach to synthesise the evidence (i.e. to assess and summarise the information provided in the studies)? If so, provide details.	N	
	Does the organisation assess the overall certainty of the evidence and reach recommendations? If so, provide details.	N	
	Derivation of health-based guideline values		
	Is there justification for the choice of uncertainty and safety factors?	Y	Yes.
	Are the parameter value assumptions documented and explained?	Y	Yes.
	Are the mathematical workings/algorithms clearly documented and explained?	Y	Yes.
	Does the organisation take into consideration non-health related matters to account for feasibility of implementing the guideline values (e.g. measurement attainability)?	NA	No, non-health related matters do not appear to be considered in guideline development. Recorded as 'not applicable'.
	Is there documentation directing use of mechanistic, mode of action, or key events in adverse outcome pathways in deriving health-based guideline values?	Y	Yes, there is a specific section that discusses these aspects for each vitamin/mineral.
	What processes are used when expert judgement is required and applied? Is the process documented and published?	?	Not specifically stated in document.
	Is dose response modelling (e.g. BMDL) routinely used?	?	No, does not appear to be routinely used in this report.
	What is the organisation's policy for dealing with substances for which a non-threshold mode of action may be applicable in humans? Has the policy been articulated and recorded?	?	Not specified in report.
	If applicable: For carcinogens, what is the level of cancer risk used by the organisation to set the health-based guideline value?	NA	-

Summary:
Total # of 'Must-Have' criteria met (or not applicable): 15/20 = 75%
Total # of 'Should-Have' criteria met (or not applicable): 5/10 = 50%
Total # of 'May-Have' criteria met (or not applicable): 0/2 = 0%

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